I, Elena Morandi,

of Via G.Mameli 6 - BUSTO ARSIZIO (VA) - ITALY, do solemnly and sincerely declare that I well understand the Italian and the English languages and that the foregoing is a full, true and faithful translation carried out by me on May 5, 1995 having title: "QUINOLINE DERIVATIVES",

of the Italian patent application N. MI95A000494 filed on 14 March 1995.

Milan, May 8, 1995.

SIGNATURE: Elena Morandi

#11

MODULARIO
I.C.A. - 101

Mod. C.E. - 1-4-7

MINISTERO DELL'INDUSTRIA, DEL COMMERCIO E DELL'ARTIGIANATO

DIREZIONE GENERALE DELLA PRODUZIONE INDUSTRIALE
UFFICIO CENTRALE BREVETTI

MARCA DA BOLLO
LIRE 15000

Autenticazione di copia di documenti relativi alla domanda di brevetto per INV. IND.

N. MI94 A 001099

Si dichiara che l'unita copia è conforme ai documenti originali depositati con la domanda di brevetto sopraspecificata, i cui dati risultano dall'accluso processo verbale di deposito.

Roma, lì ....

IL DIRETTORE DELLA DIVISIONE

IL PRIMO DIRIGENTE
(Dr. Giuseppe Petrucci)

Roma - Istituto Poligrafico e Zecca dello Stato - S.

AL MINISTERO DELL'INDUSTRIA DEL COMMERCIO E DELL'ARTIGIANATO — MODULO A — marca da bollo

UFFICIO ITALIANO BREVETTI E MARCHI - ROMA

DOMANDA DI BREVETTO PER INVENZIONE INDUSTRIALE, DEPOSITO RISERVE, ANTICIPATA ACCESSIBILITÀ AL PUBBLICO

A. RICHIEDENTE (I) — N.G.

1) Denominazione: SmithKline Beecham Farmaceutici S.p.A. — SP

Residenza: Baranzate di Bollate (Milano) — codice: 03524320151

2) Denominazione:

Residenza: — codice:

B. RAPPRESENTANTE DEL RICHIEDENTE PRESSO L'U.I.B.M.

cognome nome: Bianchetti Giuseppe ed altri — cod. fiscale:

denominazione studio di appartenenza: Studio Consulenza Brevettuale s.r.l.

via Rossini — n. 8 — città Milano — cap 20122 — (prov) MI

C. DOMICILIO ELETTIVO destinatario

via — n. — città — cap — (prov)

D. TITOLO — classe proposta (sez/cl/scl) C07D — gruppo/sottogruppo 215/00

"Derivati chinolinici"

ANTICIPATA ACCESSIBILITÀ AL PUBBLICO: SI — NO — SE ISTANZA: DATA / / — N° PROTOCOLLO

E. INVENTORI DESIGNATI — cognome nome

1) Farina Carlo

2) Giardina Giuseppe

3) Grugni Mario

4) Raveglia Luca

F. PRIORITÀ

	nazione o organizzazione	tipo di priorità	numero di domanda	data di deposito	allegato S/R	SCIOGLIMENTO RISERVE Data	N° Protocollo
1)				/ /		/ /	
2)				/ /		/ /	

G. CENTRO ABILITATO DI RACCOLTA COLTURE DI MICRORGANISMI, denominazione

H. ANNOTAZIONI SPECIALI

MARCA DA BOLLO — LIRE 15000

DOCUMENTAZIONE ALLEGATA

	N. es.				SCIOGLIMENTO RISERVE Data	N° Protocollo
Doc. 1)	1	PROV	n. pag. 44	riassunto con disegno principale, descrizione e rivendicazioni (obbligatorio 1 esemplare)	/ /	
Doc. 2)	0	PROV	n. tav.	disegno (obbligatorio se citato in descrizione, 1 esemplare	/ /	
Doc. 3)	0	RIS		lettera d'incarico, procura o riferimento procura generale	/ /	
Doc. 4)	1	RIS		designazione inventore	/ /	
Doc. 5)	0	RIS		documenti di priorità con traduzione in italiano	confronta singole priorità	
Doc. 6)	0	RIS		autorizzazione o atto di cessione	/ /	
Doc. 7)	0			nominativo completo del richiedente		

8) attestati di versamento, totale lire ~~cinquecentosessantacinquemila#~~ — obbligatorio

COMPILATO IL 27/05/1994 — FIRMA DEL(I) RICHIEDENTE (I) Minoja Fabrizio

CONTINUA SI/NO NO — Fabrizio Minoja

DEL PRESENTE ATTO SI RICHIEDE COPIA AUTENTICA SI/NO SI

UFFICIO PROVINCIALE IND. COMM. ART. DI Milano — codice 15

VERBALE DI DEPOSITO — NUMERO DI DOMANDA MI 94/A 001099 — Reg.A

L'anno millenovecento NOVANTAQUATTRO, il giorno VENTISETTE, del mese di MAGGIO

il(i) richiedente(i) sopraindicato(i) ha(hanno) presentato a me sottoscritto la presente domanda, corredata di n. 00 fogli aggiuntivi per la concessione del brevetto soprariportato.

I. ANNOTAZIONI VARIE DELL'UFFICIALE ROGANTE

IL DEPOSITANTE — timbro dell'ufficio — L'UFFICIALE ROGANTE

AL MINISTERO DELL'INDUSTRIA DEL COMMERCIO E DELL'ARTIGIANATO — MODULO A

UFFICIO ITALIANO BREVETTI E MARCHI - ROMA

DOMANDA DI BREVETTO PER INVENZIONE INDUSTRIALE, DEPOSITO RISERVE, ANTICIPATA ACCESSIBILITÀ AL PUBBLICO

A. RICHIEDENTE (I)

1) Denominazione: SmithKline Beecham Farmaceutici S.p.A.

Residenza: Baranzate di Bollate Milano — codice

2) Denominazione:

Residenza: — codice

CAMERA DI COMMERCIO INDUSTRIA ARTIGIANATO E AGRICOLTURA DI MILANO — DIRITTI DI SEGRETERIA — L. 100

MARCA DA BOLLO — LIRE 1.000

B. RAPPRESENTANTE DEL RICHIEDENTE PRESSO L'U.I.B.M.

cognome nome: Bianchetti Giuseppe ed altri

denominazione studio di appartenenza: Studio

via: Rossini — n. — città: Milano

C. DOMICILIO ELETTIVO destinatario

via — n. — città

D. TITOLO — classe proposta (sez/cl/scl): C07D — gruppo/sottogruppo: 213/

COPIA AUTENTICA

ANTICIPATA ACCESSIBILITÀ AL PUBBLICO: SI / NO

p. Il Direttore
(Pier Daniele Melegari)

Il Capo dell'Ufficio Brevetti
(Norma Sario)

Min. Ind. Comm. e Art. - U.P.I.C.A. - Milano - Serv. Brevetti

E. INVENTORI DESIGNATI — cognome nome

F. PRIORITÀ — nazione o organizzazione — tipo di priorità — numero di domanda — data di deposito — allegato S/R

G. CENTRO ABILITATO DI RACCOLTA COLTURE DI MICROORGANISMI, denominazione

H. ANNOTAZIONI SPECIALI

DOCUMENTAZIONE ALLEGATA — SCIOGLIMENTO RISERVE: Data, N° Protocollo

	N. es.			
Doc. 1)		PROV	n. pag.	riassunto con disegno principale, descrizione e rivendicazioni (obbligatorio 1 esemplare)
Doc. 2)		PROV	n. tav.	disegno (obbligatorio se citato in descrizione, 1 esemplare)
Doc. 3)		RIS		lettera d'incarico, procura o riferimento procura generale
Doc. 4)	1	RIS		designazione inventore
Doc. 5)	0	RIS		documenti di priorità con traduzione in italiano
Doc. 6)	0	RIS		autorizzazione o atto di cessione
Doc. 7)	0			nominativo completo del richiedente

confronta singole priorità

8) attestati di versamento, totale lire: cinquecentoessantacinquemila# — obbligatorio

COMPILATO IL 27/05/1994 — FIRMA DEL(I) RICHIEDENTE(I): Minoja Fabrizio

Fabrizio Minoja

CONTINUA SI/NO: NO

DEL PRESENTE ATTO SI RICHIEDE COPIA AUTENTICA SI/NO: SI

UFFICIO PROVINCIALE IND. COMM. ART. DI: Milano — codice: 15

VERBALE DI DEPOSITO — NUMERO DI DOMANDA: MI 94/A 001099 — Reg. A

L'anno millenovecento NOVANTAQUATTRO, il giorno VENTISETTE, del mese di MAGGIO

il(i) richiedente(i) sopraindicato(i) ha(hanno) presentato a me sottoscritto la presente domanda, corredata di n. 00 fogli aggiuntivi per la concessione del brevetto soprariportato.

I. ANNOTAZIONI VARIE DELL'UFFICIALE ROGANTE

IL DEPOSITANTE

PROSPETTO A

MARCA DA BOLLO
LIRE 15000

RIASSUNTO INVENZIONE CON DISEGNO PRINCIPALE, DESCRIZIONE E RIVENDICAZIONE

NUMERO DOMANDA MI94A 001099 REG. B DATA DI DEPOSITO 27 05 1994

NUMERO BREVETTO DATA DI RILASCIO

D. TITOLO

"Derivati chinolinici"

L. RIASSUNTO

Si descrivono nuovi derivati chinolinici, i procedimenti per la loro preparazione e il loro uso in medicina nel trattamento di disturbi polmonari, disturbi della pelle e prurito, infiammazione neurogenica e disturbi del SNC.

M. DISEGNO

4382 M Descrizione dell'invenzione industriale avente per titolo:

MAB/sd **"DERIVATI CHINOLINICI"**

a nome: **SmithKline Beecham Farmaceutici S.p.A.**

* * *

La presente invenzione ha per oggetto nuovi derivati chinolinici, i procedimenti per la loro preparazione e il loro uso in medicina.

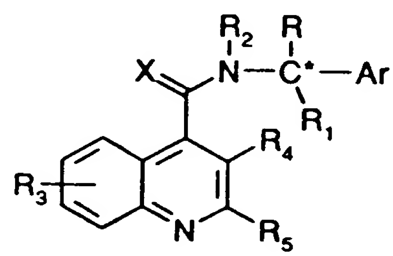
La Neurokinina B (NKB), un peptide dei mammiferi, appartiene alla famiglia dei peptidi della Tachikinina (TK), che comprende anche la Sostanza P (SP) e la Neurokinina A (NKA). Prove farmacologiche e di biologia molecolare hanno dimostrato l'esistenza di tre sottotipi di recettore TK (NK_1, NK_2 e NK_3): la NKB si lega di preferenza al recettore NK_3, quantunque riconosca anche gli altri due recettori, seppure con una minore affinità (Maggi et al, **1993**, J. Auton. Pharmacol., 13, 23-93).

Sono noti antagonisti selettivi peptidici del recettore NK_3 (Drapeau, **1990**, Regul. Pept., 31, 125-135) e le evidenze sugli agonisti peptidici del recettore NK_3 suggeriscono che NKB, attivando il recettore NK_3, svolga un ruolo fondamentale nella modulazione dell'input neuronale a livello di vie respiratorie, pelle, colonna vertebrale e vie nigro-striatali (Myers and Undem, **1993**, J. Phisiol., 470, 665-679; Counture et al., **1993**, Regul. Peptides, 46, 426-429; Mccarson and Krause, **1994**, J. Neurosci., 14(2), 712-720; Arenas et al,. **1991**, J. Neurosci., 11, 2332-8).

Tuttavia, la natura peptide-simile degli antagonisti noti, li rende probabilmente troppo labili, dal punto di vista metabolico, per servire come agenti terapeutici nella pratica.

Abbiamo ora trovato una nuova classe di antagonisti selettivi non-peptidici del recettore NK_3, di gran lunga più stabili dal punto di vista metabolico degli antagonisti peptidici del recettore NK_3, e di potenziale utilità terapeutica nel trattamento di disturbi polmonari (asma, malattie polmonari ostruttive croniche -COPD-, iperreattività delle vie respiratorie, tosse), disturbi della pelle e prurito (per esempio dermatite atopica, vesciche, ustioni e bruciori cutanei), infiammazione neurogenica e disturbi del SNC (morbo di Parkinson, disturbi motori, ansia).

Secondo la presente invenzione, viene fornito un composto, o un suo sale o solvato, di formula generale (I):



(I)

in cui:

Ar è un fenile o naftile eventualmente sostituito o un gruppo eterociclico ad anello singolo o fuso, eventualmente sostituito, di carattere aromatico, contenente da 5 a 12 atomi d'anello e comprendente fino a quattro eteroatomi nell'anello o in ciascun anello, scelti tra S, O, N; con la condizione che Ar non sia p-isobutilfenile; R è C_{1-6} alchile lineare o ramificato, C_{3-7} cicloalchile, C_{4-7} cicloalchilalchile, fenile eventualmente sostituito, anelli eteroaromatici eventualmente sostituiti a 5-elementi, comprendenti fino a quattro eteroatomi

scelti tra O o N, idrossi C_{1-6} alchile, ammino C_{1-6} alchile, C_{1-6} alchilamminoalchile, di C_{1-6} alchilamminoalchile, C_{1-6} acilamminoalchile, C_{1-6} alcossialchile, C_{1-6} alchilcarbonile, carbossi, C_{1-6} alcossicarbonile, amminocarbonile, C_{1-6} alchilamminocarbonile, di C_{1-6} alchilamminocarbonile, alogeno C_{1-6} alchile;

R_1 e R_2, che possono essere uguali o diversi, sono indipendentemente idrogeno o C_{1-6} alchile lineare o ramificato, oppure insieme formano un gruppo $-(CH_2)_n-$ in cui n rappresenta 3, 4 o 5;

R_3 e R_4, che possono essere uguali o diversi, sono indipendentemente idrogeno, C_{1-6} alchile lineare o ramificato, C_{1-6} alchenile, arile, C_{1-6} alcossi, idrossi, alogeno, nitro, ciano, carbossi, carbossammido, solfonammido, C_{1-6} alcossicarbonile o trifluorometile, con fino a quattro sostituenti R_3 nel nucleo chinolinico;

R_5 è C_{1-6} alchile lineare o ramificato, C_{3-7} cicloalchile, C_4-C_7 cicloalchilalchile, arile eventualmente sostituito, o un gruppo eterociclico ad anello singolo o fuso, eventualmente sostituito, di carattere aromatico, contenente da 5 a 12 atomi nell'anello e comprendente fino a quattro eteroatomi nell'anello o in ciascun anello, scelti tra S, O, N; X è O, S o N-C≡N.

Preferibilmente Ar è fenile eventualmente sostituito da idrossi, alogeno, C_{1-6} alcossi o trifluorometile. Esempi di alogeno sono cloro e fluoro, e un esempio di C_{1-6} alcossi è metossi.

Esempi di Ar come gruppo eterociclico sono furile, tienile, piridile, pirrile, tiazolile, indolile, benzofurile o benzotienile.

Esempi di R sono i seguenti:

C_{1-6} alchile: metile, etile, n-propile, iso-propile;

C_{3-7} cicloalchile: ciclopropile;

C_{4-7} cicloalchilalchile: ciclopropilmetile;

anelli eteroaromatici: ossadiazoli, metilossadiazoli;

idrossi C_{1-6}alchile: $-CH_2OH$, $-CH_2CH_2OH$, $CH(Me)OH$, $CH_2CH(Me)OH$;

ammino C_{1-6} alchile: $-CH_2NH_2$;

C_{1-6} alchilamminoalchile: $-CH_2NHMe$, $-CH_2NHEt$;

di C_{1-6} alchilamminoalchile: $-CH_2NHMe_2$, $-CH_2NHEt_2$;

C_{1-6} acilamminoalchile: $-CH_2NHCOMe$;

C_{1-6} alcossilalchile: CH_2OMe;

C_{1-6} alchilcarbonile: COMe;

C_{1-6} alcossicarbonile: COOMe; COOEt; -COOi-Pr;

C_{1-6} alchilamminocarbonile: -CONHMe, -CONHEt;

di C_{1-6} alchilamminocarbonile: $CONMe_2$, $CONEt_2$, -CONMeEt;

alogeno C_{1-6} alchile: trifluorometile.

Esempi di R_1 e R_2 sono metile, etile e n-propile.

Esempi di R_3 e R_4 sono metile, etile, n-propile, metossi, etossi, cloro, fluoro, bromo e metossicarbonile.

Esempi di R_5 sono iso-propile, ciclopentile, cicloesile, ciclopentilmetile, cicloesilmetile, fenile eventualmente sostituito come definito sopra per Ar, e i gruppi eterociclici come definiti sopra per Ar.

Un sottogruppo preferito di composti nell'ambito della formula (I) è quello di formula (Ia):------------------------------------

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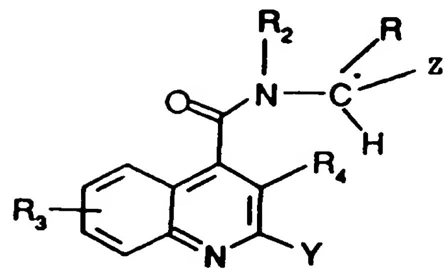
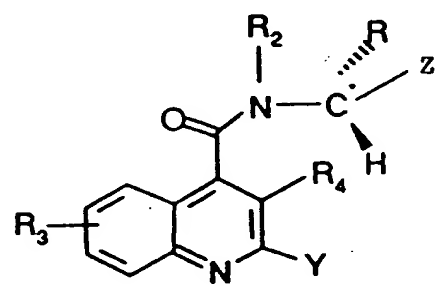


(Ia)

in cui:

R, R_2, R_3 e R_4 sono come definiti nella formula (I) e Y e Z, che possono essere uguali o diversi, sono ciascuno Ar come definito nella formula (I).

Un gruppo particolarmente preferito di composti di formula (Ia) sono quelli di formula (Ib), in cui il gruppo R è orientato verso il basso e H verso l'alto, rispetto al piano N-C-Z.



(Ib)

I composti di formula (I) o i loro sali o solvati sono preferibilmente in forma farmaceuticamente accettabile o sostanzialmente pura. Per forma farmaceuticamente accettabile si intende, tra l'altro, di un livello di purezza farmaceuticamente accettabile, con esclusione dei normali eccipienti farmaceutici quali diluenti e veicoli, e non comprendente materiale considerato tossico ai normali livelli di dosaggio.

Una forma sostanzialmente pura conterrà generalmente almeno il 50%

(con esclusione di normali additivi farmaceutici), preferibilmente il 75%, più preferibilmente il 90% e ancora più preferibilmente il 95% del composto di formula (I) o suo sale o solvato.

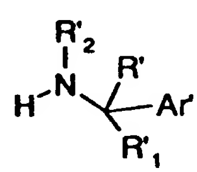
Una forma farmaceuticamente accettabile preferita è la forma cristallina, compresa tale forma in una composizione farmaceutica. Nel caso di sali e solvati, anche le porzioni ioniche e solventi aggiuntive devono essere non tossiche.

Esempi di sali farmaceuticamente accettabili di un composto di formula (I) comprendono i sali di addizione acida con acidi farmaceutici convenzionali, per esempio acido maleico, cloridrico, bromidrico, fosforico, acetico, fumarico, salicilico, citrico, lattico, mandelico, tartarico, succinico, benzoico, ascorbico e metansolfonico.

Esempi di solvati farmaceuticamente accettabili di un composto di formula (I) comprendono gli idrati.

I composti di formula (I) hanno almeno un centro asimmetrico e pertanto esistono in più di una forma stereoisomera. L'invenzione si estende a tutte tali forme e alle loro miscele, racemati inclusi.

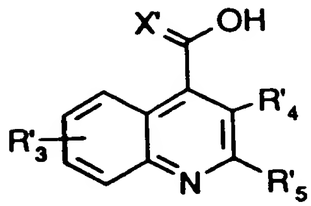
L'invenzione fornisce anche un procedimento per la preparazione di un composto di formula (I), che comprende la reazione di un composto di formula (III)



(III)

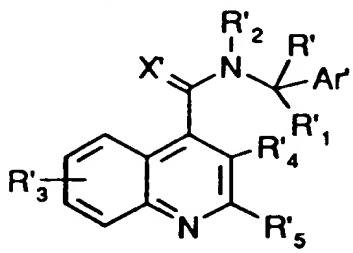
in cui R', R'_1, R'_2 e Ar' sono R, R_1, R_2 e Ar come definiti per la formula (I), oppure un gruppo o un atomo convertibili in R, R_1, R_2 e Ar,

con un composto di formula (II)



(II)

o un suo derivato attivo, in cui R'_3, R'_4, R'_5 e X' sono R_3, R_4, R_5 e X, come definiti per la formula (I), o un gruppo convertibile in R_3, R_4, R_5 e X, per formare un composto di formula (Ic)



(Ic)

ed eventualmente in seguito realizzazione di uno o più degli stadi seguenti:

(a) dove R', da R'_1 a R'_5, Ar' e X' sono diversi da R, da R_1 a R_5, Ar e X, conversione di uno qualsiasi di R', da R'_1 a R'_5, Ar' e X' in R, da R_1 a R_5, Ar e X, per ottenere un composto di formula (I),

(b) dove R', da R'_1 a R'_5, Ar' e X' sono R, da R_1 a R_5, Ar e X, conversione di uno qualsiasi di R, da R_1 a R_5, Ar e X in un altro R, da R_1 a R_5, Ar e X, per ottenere un composto di formula (I),

(c) formazione di un sale e/o un solvato del composto di formula (Ic) ottenuto.

Derivati attivi adatti dei composti di formula (II) sono gli alogenuri acilici (di preferenza i cloruri), le azidi di acidi o le anidridi di acidi. Un altro derivato adatto è l'anidride mista formata

tra l'acido e un alchilcloroformiato; un altro derivato adatto è l'estere attivato, come cianometil estere, tiofenil estere, p-nitrofenil estere, p-nitrotiofenil estere, 2,4,6-triclorofenil estere, pentaclorofenil estere, pentafluorofenil estere, N-idrossi-ftalimmido estere, N-idrossipiperidino estere, N-idrossisuccinimmido estere, N-idrossibenzotriazol estere; oppure il gruppo carbossi può essere attivato usando una carbodiimmide o N,N'-carbonildiimidazolo.

Per esempio, in metodi standard ben noti all'esperto della materia, i composti di formula (III) possono essere copulati:

(a) con un cloruro acilico in presenza di una base inorganica o organica, in un solvente aprotico adatto quale dimetilformammide (DMF) a una temperatura nell'intervallo da -70 a 50°C (di preferenza in un intervallo da -10 a 20°C),

(b) con l'acido in presenza di un agente condensante adatto, come per esempio N,N-carbonildiimidazolo (CDI) o una carbodiimmide quale dicicloesilcarbodiimmide (DCC) o N-dimetilamminopropil-N'-etilcarbodiimmide e N-idrossibenzotriazolo (HOBT) per rendere massime le rese ed evitare processi di racemizzazione (Synthesis, 453, 1972) in un solvente aprotico come una miscela di acetonitrile (MeCN) e tetraidrofurano (THF) in un rapporto da 1:9 a 7:3, rispettivamente, a una temperatura nell'intervallo da -70 a 50°C (preferibilmente in un intervallo da -10 a 25°C) (vedi Schema 1). ---------------------

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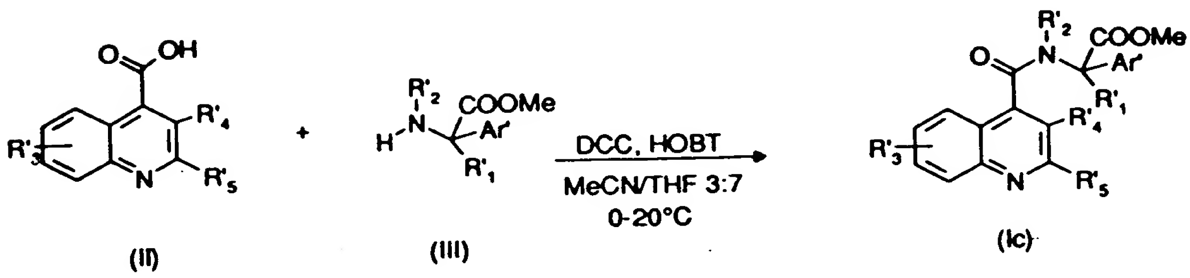
Schema 1



(c) con un'anidride mista generata in situ dall'acido e da un alchil (per esempio isopropil) cloroformiato in un solvente aprotico adatto come il diclorometano, a una temperatura in un intervallo da -70 a 50°C (preferibilmente in un intervallo da -20 a 20°C).

Si noterà che un composto di formula (Ic) può essere convertito in un composto di formula (I), o che un composto di formula (I) può essere convertito in un altro composto di formula (I), per interconversione di sostituenti adatti. Pertanto, certi composti di formula (I) e (Ic) sono intermedi utili nella formazione di altri composti della presente invenzione.

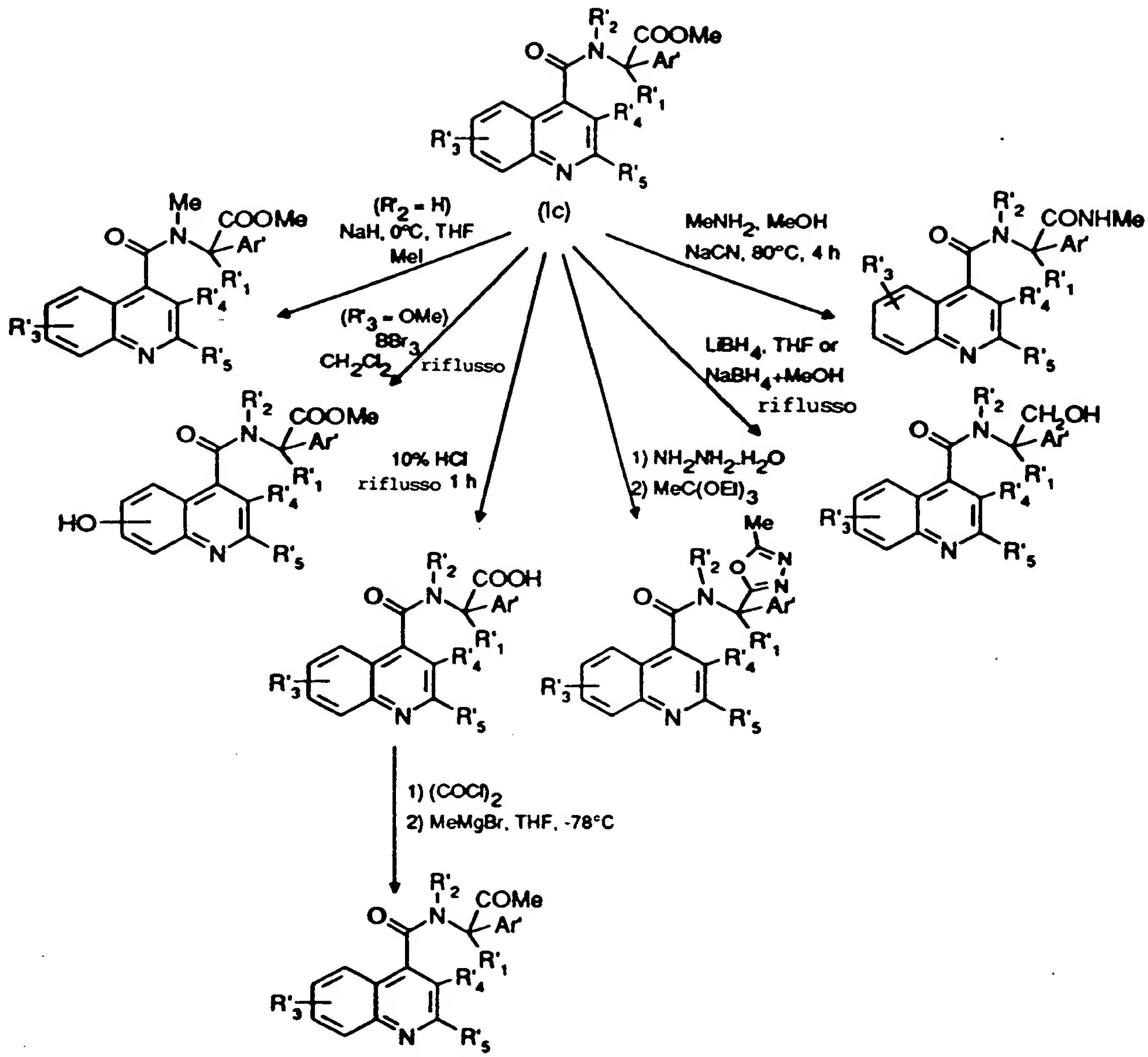
Per esempio R'_2 può essere idrogeno e convertito in gruppo alchile R_2, per esempio metile, mediante procedure convenzionali di alchilazione all'ammide (Zabicky, The chemistry of amides; Interscience, London, **1970**, p. 749). Quando X' è ossigeno, esso può essere convertito in X zolfo con reagenti standard per la formazione di tioammidi, come P_2S_5 (Chem. Rev., 61, 45, **1961** o Angew. Chem., 78, 517, **1966**) oppure il reagente di Lawesson (Tetrahedron, 41, 5061, **1985**). Quando Ar' o R'_5 è un fenile metossi-sostituito, esso può essere convertito in un altro Ar' o R'_5 fenile idrossi-sostituito con procedure standard di demetilazione

attraverso acidi di Lewis, come il tribromuro di bromo (Synthesis, 249, **1983**) oppure con acidi minerali, come l'acido bromidrico o iodidrico. Quando R è un gruppo alcossicarbonile, per esempio metossicarbonile, esso può essere convertito in un altro R, quale etossicarbonile, mediante transesterificazione con un alcol appropriato ad una temperatura in un intervallo da 20 a 120°C; carbossi per idrolisi in mezzo acido o basico; amminocarbonile, alchilamminocarbonile o dialchilamminocarbonile per transammidazione con ammoniaca, un'ammina primaria o un'ammina secondaria in metanolo come solvente ad una temperatura in un intervallo da 10 a 120°C, eventualmente in presenza di una quantità catalitica di NaCN (J. Org. Chem., 52, 2033, **1987**) oppure utilizzando trimetilalluminio (Me_3Al) (Tetrahedron Letters, 48, 4171, **1977**); idrossimetile mediante riduzione selettiva con un idruro metallico, quale riduzione con boroidruro di litio, (Tetrahedron, 35, 567, **1979**) oppure riduzione con boroidruro di sodio in THF + MeOH (Bull. Chem. Soc. Japan, 57, 1948, **1984** o Synth. Commun., 12, 463, **1982**); alchilcarbonile per formazione di un cloruro acilico e successiva reazione con alogenuri di alchilmagnesio in THF come solvente, ad una temperatura in un intervallo da -78 a 30°C (Tetrahedron Letters, 4303, **1979**), oppure con alogenuri di alchilcadmio o dialchilcadmio in presenza di $MgCl_2$ o LiCl (J. Org. Chem., 47, 2590, **1982**). Un altro gruppo in cui R' come metossicarbonile può essere convertito è un anello eteroaromatico sostituito, come un ossadiazolo (J. Med. Chem., 34, 2726, **1991**).

Lo Schema 2 riassume alcune procedure sopra descritte per convertire un composto di formula (Ic) o (I), in cui X' è ossigeno, R' è

COOMe, Ar' e da R'_1 a R'_5 sono come descritti nella formula (I), in un altro composto di formula (I).

Schema 2



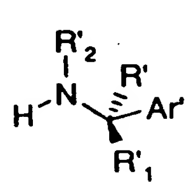
I composti di formula (I) possono essere convertiti nei loro sali di addizione con acidi farmaceuticamente accettabili per reazione con gli acidi organici o minerali appropriati.

I solvati dei composti di formula (I) possono essere formati per cristallizzazione o ricristallizzazione dal solvente appropriato. Per esempio, gli idrati possono essere formati per cristallizzazione o ri-

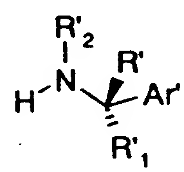
cristallizzazione da soluzioni acquose o da soluzioni in solventi organici contenenti acqua.

Anche i sali o solvati dei composti di formula (I) che non sono farmaceuticamente accettabili, possono essere utili come intermedi nella produzione di sali o solvati farmaceuticamente accettabili. Di conseguenza anche tali sali o solvati fanno parte di questa invenzione.

Come sopra menzionato, i composti di formula (I) esistono in più di una forma stereoisomera e il procedimento dell'invenzione produce racemati così come forme enantiomericamente pure. Per ottenere gli enantiomeri puri, ammine primarie o secondarie appropriate enantiomericamente pure di formula (IIId) o (IIIe)

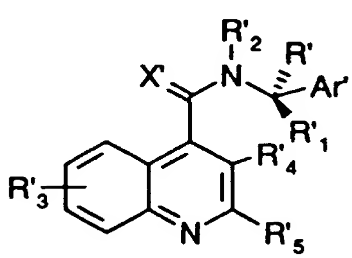


(IIId)

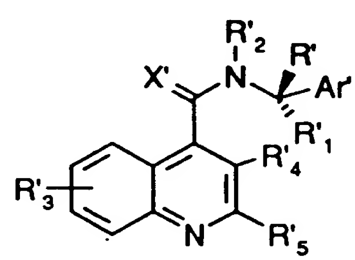


(IIIe)

vengono fatte reagire con i composti di formula (II), per ottenere i composti di formula (I'd) o (I'e).

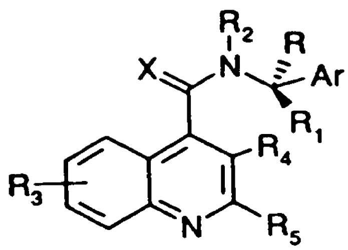


(I'd)

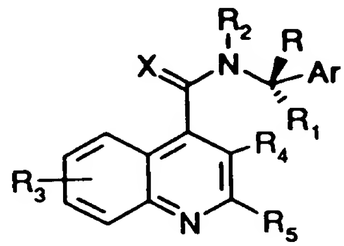


(I'e)

I composti di formula (I'd) o (I'e) possono successivamente essere convertiti nei composti di formula (Id) o (Ie) con i metodi di conversione sopra menzionati.



(Id)



(Ie)

I composti di formula (II) sono composti noti oppure possono essere preparati da composti noti con metodi noti.

Per esempio, il composto di formula (II) in cui X' è ossigeno, R'_3, R'_4 e R'_5 sono idrogeno, è descritto in Pfitzinger, J. Prakt. Chem., 38, 582, **1882** e in Pfitzinger, J. Prakt. Chem., 56, 293, **1897**; il composto di formula (II) in cui X' è ossigeno, R'_3 e R'_4 sono idrogeno e R'_5 è 2-piridile è descritto in Risaliti, Ric. Scient., 28, 561, **1958**; i composti di formula (II) in cui X' è ossigeno, R'_3 e R'_4 sono idrogeno e R'_5 è o-, m- e p-clorofenile, o-fluorofenile e 3,4-diclorofenile sono descritti in Brown et al., J. Am. Chem. Soc., 68, 2705, **1946**; il composto di formula (II), in cui X' è ossigeno, R'_3 e R'_4 sono idrogeno e R'_5 è p-metossifenile è descritto in Ciusa e Luzzatto, Gazz. Chim. Ital., 44, 64, **1914**; il composto di formula (II), in cui X' è ossigeno, R'_3 e R'_4 sono idrogeno e R'_5 è m-trifluorometilfenile è descritto in Shargier and Lalezari, J. Chem. Eng. Data, 8, 276, **1963**; il composto di formula (II), in cui X' è ossigeno, R'_3 e R'_4 sono idrogeno e R'_5 è p-fluorofenile è descritto in Bu Hoi et al., Rec. Trav. Chim., 68, 781, **1949**; il composto di formula (II), in cui X' è ossigeno, R'_3 e R'_4 sono idrogeno e R'_5 è p-metilfenile è descritto in Prevost et al., Compt. Rend. Acad. Sci., 258, 954, **1964**; il composto di formula (II), in cui X'

è ossigeno, R'_3 e R'_4 sono idrogeno e R'_5 è p-bromofenile è descritto in Nicolai et al., Eur. J. Med. Chem., 27, 977, **1992**; il composto di formula (II), in cui X' è ossigeno, R'_4 e R'_5 sono idrogeno e R'_3 è 6-metile è descritto in Buchmann and Howton, J. Am. Chem. Soc., 68, 2718, **1946**; il composto di formula (II), in cui X' è ossigeno, R'_4 e R'_5 sono idrogeno e R'_3 è 8-nitro è descritto in Buchmann et al., J. Am. Chem. Soc., 69, 380, **1947**; il composto di formula (II), in cui X' è ossigeno, R'_4 è idrogeno, R'_3 è 6-cloro, R'_5 è p-clorofenile è descritto in Lutz et al., J. Am. Chem. Soc., 68, 1813, **1946**; il composto di formula (II), in cui X' è ossigeno, R'_3 e R'_4 sono idrogeno e R'_5 è 2-tiazolile è descritto nella domanda di brevetto europeo EP 112,776; i composti di formula (II), in cui X' è ossigeno, R'_3 è 8-trifluorometile, R'_4 è idrogeno e R'_5 è fenile, o- e p-fluorofenile, 3,4-diclorofenile, p-metossifenile sono descritti in Nicolai et al., Eur. J. Med. Chem., 27, 977, **1992**; i composti di formula (II), in cui X' è ossigeno, R'_3 è 6-bromo, R'_4 è idrogeno e R'_5 è fenile o p-fluorofenile sono descritti in Nicolai et al., Eur. J. Med. Chem., 27, 977, **1992**; altri composti di formula (II) sono descritti in **Ger. Offen. DE 3,721,222** e nella domanda di brevetto europeo EP 384,313.

I composti di formula (III), (IIId) e (IIIe) sono composti commercialmente disponibili oppure possono essere preparati da composti noti con metodi noti (per esempio, i composti di formula (III) in cui R' è alcossicarbonile, R'_1 e R'_2 sono idrogeno e Ar' è come definito per i composti di formula (I), sono descritti in Liebigs Ann. der Chemie, 523, 199, **1936**.

L'attività dei composti di formula (I) come antagonisti del recettore NK_3 nelle prove standard indica che essi sono di potenziale utilità terapeutica nel trattamento di disturbi polmonari (asma, COPD, iperreattività delle vie respiratorie, tosse), disturbi della pelle e prurito (dermatite atopica, vesciche, ustioni e bruciori cutanei), infiammazione neurogenica e disturbi del SNC (morbo di Parkinson, disturbi motori, ansia) (d'ora in avanti indicati come "Condizioni").

Di conseguenza, la presente invenzione fornisce anche un composto di formula (I), o un suo sale o solvato farmaceuticamente accettabile, per uso come sostanza terapeuticamente attiva.

La presente invenzione fornisce inoltre una composizione farmaceutica che comprende un composto di formula (I), o un suo sale o solvato farmaceuticamente accettabile, e un veicolo farmaceuticamente accettabile.

La presente invenzione fornisce anche l'uso di un composto di formula (I), o un suo sale o solvato farmaceuticamente accettabile, nella fabbricazione di un medicamento per il trattamento delle condizioni.

Tale medicamento, e una composizione dell'invenzione, possono essere preparati miscelando un composto con un opportuno veicolo, che può contenere un diluente, legante, riempitivo, disintegrante, agente aromatizzante, agente colorante, lubrificante o conservante in modo convenzionale.

Questi eccipienti convenzionali possono essere impiegati per esempio nella preparazione di composizioni di agenti noti, per il trattamento delle condizioni.

Preferibilmente, una composizione farmaceutica dell'invenzione è in forma di dosaggio unitario e in una forma adatta per l'uso nel campo medico o veterinario. Per esempio, tali preparazioni possono essere in forma confezionata accompagnata da istruzioni scritte o stampate per uso come agente nel trattamento di ognuna delle condizioni.

L'intervallo di dosaggio adatto per i composti dell'invenzione dipende dal composto che sarà impiegato e dalle condizioni del paziente. Esso dipenderà anche, tra l'altro, dalla relazione tra la potenza e l'assorbibilità, dalla frequenza e dalla via di somministrazione.

Il composto o composizione dell'invenzione può essere formulato per qualsiasi via di somministrazione ed è preferibilmente in forma di dosaggio unitario o in una forma tale che un paziente umano possa autosomministrarsela in un singolo dosaggio. Vantaggiosamente, la composizione è adatta per la somministrazione orale, rettale, topica, parenterale, endovenosa o intramuscolare. Le preparazioni possono essere formulate per dare un lento rilascio del principio attivo.

Le composizioni possono essere, per esempio, sotto forma di compresse, capsule, bustine, fiale, polveri, granuli, pastiglie, polveri ricostituibili, o preparazioni liquide, per esempio soluzioni o sospensioni, o supposte.

Le composizioni, per esempio quelle adatte per la somministrazione orale, possono contenere eccipienti convenzionali quali agenti leganti, per esempio sciroppo, acacia, gelatina, sorbitolo, adragante, o polivinilpirrolidone; riempitivi, per esempio lattosio, zucchero, amido di mais, fosfato di calcio, sorbitolo o glicina; lubrificanti per compres-

satura, per esempio stearato di magnesio; disintegranti, per esempio amido, polivinilpirrolidone, amido sodio glicolato o cellulosa microcristallina; o agenti indurenti farmaceuticamente accettabili quali sodio laurilsolfato.

Le composizioni solide possono essere ottenute con metodi convenzionali di miscelazione, riempimento, compressatura o simili. Possono essere usate ripetute operazioni di miscelazione per distribuire il principio attivo in quelle composizioni che impiegano grandi quantità di riempitivi. Quando la composizione è sotto forma di compressa, polvere o pastiglia, può essere usato qualsiasi veicolo adatto per la formulazione di composizioni farmaceutiche solide, per esempio stearato di magnesio, amido, glucosio, lattosio, saccarosio, farina di riso e gesso.

Le compresse possono essere rivestite secondo metodi noti nella normale pratica farmaceutica, in particolare con rivestimenti gastroresistenti. La composizione può anche essere sotto forma di capsula da deglutire, per esempio di gelatina contenente il composto, se desiderato con un veicolo o altri eccipienti.

Le composizioni liquide per la somministrazione orale possono essere sotto forma, per esempio, di emulsioni, sciroppi o elisir, o possono essere presentate come prodotto secco da ricostituire con acqua o altro veicolo opportuno prima dell'uso. Tali composizioni liquide possono contenere additivi convenzionali quali agenti sospendenti, per esempio sorbitolo, sciroppo, metilcellulosa, gelatina, idrossietilcellulosa, carbossimetilcellulosa, gel di stearato di alluminio, grassi commestibili idrogenati; agenti emulsionanti, per esempio lecitina, sor-

bitan monooleato, o gomma acacia; veicoli acquosi o non acquosi, che comprendono oli commestibili, per esempio, olio di mandorle, olio di cocco frazionato, esteri oleosi, per esempio, esteri di glicerina, o glicol propilenico, o alcol etilico, glicerina, acqua o soluzione fisiologica; conservanti, per esempio p-idrossibenzoato di metile o di propile o acido sorbico; e, se desiderato, convenzionali agenti aromatizzanti o coloranti.

I composti di questa invenzione possono anche essere somministrati attraverso una via non orale. Secondo la consueta procedura farmaceutica, le composizioni possono essere formulate, per esempio per la somministrazione rettale come supposta. Esse possono anche essere formulate, per la presentazione sotto forma iniettabile, in una soluzione, sospensione o emulsione acquosa o non acquosa, in un liquido farmaceuticamente accettabile, per esempio acqua sterile apirogena o olio accettabile per somministrazione parenterale o una miscela di liquidi. Il liquido può contenere agenti batteriostatici, antiossidanti o altri conservanti, tamponi o soluti per rendere la soluzione isotonica con il sangue, agenti ispessenti, agenti sospendenti o altri additivi farmaceuticamente accettabili. Tali forme saranno presentate sotto forma di dosaggio unitario quali fiale o dispositivi per iniezione monouso o in forme multidosaggio quali flaconi, dai quali può essere prelevata l'appropriata dose, o una forma solida o concentrata che può essere usata per preparare una formulazione iniettabile.

I composti di questa invenzione possono anche essere somministrati per inalazione, attraverso la via nasale o orale. Tale somministrazione

può essere effettuata con una formulazione spray comprendente un composto e un carrier opportuno, eventualmente sospeso ad esempio in un propellente idrocarburico.

Formulazioni spray preferite comprendono particelle di composto micronizzate in combinazione con un tensioattivo, solvente o agente disperdente per prevenire la sedimentazione delle particelle sospese. Preferibilmente, la granulometria del composto è da circa 2 a 10 μ.

Un'ulteriore modalità di somministrazione dei composti dell'invenzione comprende la cessione transdermica utilizzando una formulazione di cerotto cutaneo. Una formulazione preferita comprende un composto disperso in un adesivo sensibile alla pressione che aderisce alla pelle, permettendo così che il composto diffonda dall'adesivo attraverso la pelle per essere ceduto al paziente. Per una velocità costante di assorbimento percutaneo, si possono usare adesivi sensibili a pressione noti nella tecnica, quali gomma naturale o silicone.

Come sopra menzionato, la dose efficace di composto dipende dal particolare composto impiegato, dalle condizioni del paziente e dalla frequenza e via di somministrazione. Una dose unitaria generalmente conterrà da 20 a 1000 mg e preferibilmente conterrà da 30 a 500 mg, in particolare 50, 100, 150, 200, 250, 300, 350, 400, 450 o 500 mg. La composizione può essere somministrata una o più volte al giorno, per esempio 2, 3 o 4 volte al giorno, e la dose totale giornaliera per un adulto di 70 kg normalmente sarà nell'intervallo da 100 a 3000 mg. Alternativamente, la dose unitaria conterrà da 2 a 20 mg di principio attivo e sarà somministrata in dosi multiple, se desiderato, per dare la

dose giornaliera di cui sopra.

Se i composti vengono somministrati secondo l'invenzione non sono previsti effetti tossicologici inaccettabili.

La presente invenzione fornisce anche un metodo per il trattamento e/o la profilassi delle Condizioni nei mammiferi, in particolare negli esseri umani, che comprende la somministrazione al mammifero che necessita di tale trattamento e/o profilassi di una quantità efficace di un composto di formula (I) o di un suo sale o solvato farmaceuticamente accettabile.

L'attività dei composti della presente invenzione, come leganti del recettore NK_3, è determinata dalla loro capacità di inibire il legame dei leganti radiomarcati del recettore NK_3, $[^{125}I]$-[Me-Phe^7]-NKB o $[^3H]$-Senktide, ai recettori NK_3 di cavia e umani (Renzetti et al., **1991**, Neuropeptide, 18, 104-114; Buell et al., **1992**, FEBS, 299(1), 90-95; Chung et al, **1994**, Biochem. Biophys. Res. Commun., 198(3), 967-972). Le prove di legame utilizzate consentono la determinazione della concentrazione di ogni singolo composto necessaria per ridurre del 50% il legame specifico di $[^{125}I]$-[Me-Phe^7]-NKB e $[^3H]$-Senktide al recettore NK_3 in condizioni di equilibrio. Le prove di legame forniscono per ogni composto saggiato le medie dei valori di IC_{50} di 2-5 esperimenti separati realizzati in triplicato o in quadruplicato. I composti più potenti della presente invenzione mostrano valori di IC_{50} nell'intervallo di 1-1000 nM; per esempio, il composto dell'Esempio 12 mostra una IC_{50} di 66 nM (n=3) nelle membrane corticali di cavia, per spostamento di $[^3H]$-Senktide.

L'attività NK_3-antagonista dei composti della presente invenzione è determinata dalla loro capacità di inibire la contrazione dell'ileo di cavia indotta da Senktide (Maggi et al., **1990**, Br. J. Pharmacol., 101, 996-1000) e la mobilizzazione di Ca^{++} mediata da recettori NK_3 umani (Mochizuki et al., **1994**, J. Biol. Chem., 269, 9651-9658). La prova funzionale sulla cavia fornisce per ogni composto saggiato medie dei valori di K_B di 3-8 esperimenti separati, dove K_B è la concentrazione del composto individuale richiesta per produrre uno spostamento verso destra di due volte nella curva dose-risposta di Senktide.

Le prove funzionali sui recettori umani consentono la determinazione della concentrazione di ogni singolo composto necessaria per ridurre del 50% (valori di IC_{50}) la mobilizzazione del Ca^{++} indotta dall'agonista NKB. In questa prova i composti della presente invenzione si comportano da antagonisti.

Il potenziale terapeutico dei composti della presente invenzione nel trattamento delle Condizioni può essere determinato utilizzando modelli di malattia con i roditori.

Le seguenti Descrizioni illustrano la preparazione degli intermedi, mentre gli Esempi illustrano la preparazione dei composti della presente invenzione. I composti degli Esempi sono riassunti in Tabella.

DESCRIZIONE 1

2-fenil-4-chinolincarbonil cloruro

11,7 ml (136,3 mmoli) di ossalil cloruro vengono sciolti in 150 ml di CH_2Cl_2. La soluzione viene raffreddata a -10°C e vengono aggiunti, in più' porzioni, 20 g (80,2 mmoli) di acido 2-fenil-4-chinolincarbossi-

lico, commercialmente disponibile. La miscela di reazione viene lasciata a se', a temperatura ambiente, per tutta la notte e poi evaporata a secco sotto vuoto. Si ottengono 22 g del prodotto desiderato, utilizzato senza ulteriori purificazioni.

$C_{16}H_{10}ClNO$

P.M. = 267,76

DESCRIZIONE 2

acido 2-fenil-7-metossi-4-chinolincarbossilico

5 g (28,2 mmoli) di 6-metossiisatina, 4 ml (33,8 mmoli) di acetofenone e 5,2 g (92,6 mmoli) di idrossido di potassio vengono sciolti in 22,9 ml di EtOH assoluto e la sospensione viene scaldata a 80°C per 42 ore. La miscela di reazione viene raffreddata, vengono aggiunti 50 ml di acqua e la soluzione viene estratta con 50 ml di Et_2O. La fase acquosa, raffreddata con ghiaccio, viene acidificata a pH 1 con HCl al 37% e il precipitato viene raccolto per filtrazione, lavato con acqua e asciugato sotto vuoto a 40°C. Si ottengono 7,0 g del prodotto desiderato.

$C_{17}H_{13}NO_3$

P.F. = 226-228°C

P.M. = 279,30

Analisi elementare:

Calcolato: C, 73,11; H, 4,69; N, 5,01;

Trovato: C, 72,07; H, 4,59; N, 4,90.

I.R. (KBr): 3420; 1630 cm^{-1}.

DESCRIZIONE 3

2-fenil-7-metossi-4-chinolincarbonil cloruro

2,8 ml (32,3 mmoli) di ossalil cloruro vengono sciolti in 60 ml di CH_2Cl_2. La soluzione viene raffreddata a -10°C e vengono aggiunti, in più' porzioni, 6 g (19,0 mmoli) di acido 7-metossi-2-fenil-4-chinolincarbossilico. La miscela di reazione viene lasciata a se', a temperatura ambiente, per tutta la notte e poi evaporata a secco sotto vuoto. Si ottengono 7,0 g del prodotto desiderato, utilizzato senza ulteriori purificazioni.

$C_{17}H_{12}ClNO_2$

P.M. - 297,74

DESCRIZIONE 4

acido 2-fenil-7-idrossi-4-chinolincarbossilico iodidrato

1,5 g (5,4 mmoli) di acido 7-metossi-2-fenil-4-chinolincarbossilico vengono aggiunti, in più' porzioni, a 50 ml di HI al 57%. La miscela di reazione viene scaldata a ricadere sotto vigorosa agitazione magnetica per 5 ore e poi evaporata a secco sotto vuoto per fornire 2,1 g del prodotto desiderato.

$C_{16}H_{11}NO_3 \cdot HI$

P.M. - 393,17

I.R. (KBr): 3120; 1650; 1620 cm^{-1}.

DESCRIZIONE 5

acido 2-(2-tienil)-4-chinolincarbossilico

5 g (34,0 mmoli) di isatina, 4,4 ml (40,8 mmoli) di 2-acetiltiofene e 6,3 g (112,2 mmoli) di idrossido di potassio vengono sciolti in 40 ml

di EtOH assoluto e la sospensione viene scaldata a 80°C per 16 ore. La miscela di reazione viene raffreddata, vengono aggiunti 50 ml di acqua e la soluzione viene estratta con 50 ml di Et_2O. La fase acquosa, raffreddata con ghiaccio, viene acidificata a pH 1 con HCl al 37% e il precipitato viene raccolto per filtrazione, lavato con acqua, asciugato sotto vuoto a 40°C e triturato con AcOEt. Si ottengono 4,8 g del prodotto desiderato.

$C_{14}H_9NO_2S$

P.F. - 181-183°C

P.M. - 255,29

I.R. (KBr): 1620 cm^{-1}.

300 MHz ^1H-NMR (DMSO-d_6): δ 8,60 (d, 1H); 8,45 (s, 1H); 8,10 (m, 2H); 7,78 (m, 2H); 7,68 (t, 1H); 7,22 (m, 1H).

DESCRIZIONE 6

acido 2-(2-furil)-4-chinolincarbossilico

5 g (34,0 mmoli) di isatina, 4 ml (40,8 mmoli) di 2-acetilfurano e 6,3 g (112,2 mmoli) di idrossido di potassio vengono sciolti in 40,9 ml di EtOH assoluto e la sospensione viene scaldata a 80°C per 12 ore. La miscela di reazione viene raffreddata, vengono aggiunti 50 ml di acqua e la soluzione viene estratta con 50 ml di Et_2O. La fase acquosa, raffreddata con ghiaccio, viene acidificata a pH 1 con HCl al 37% e il precipitato viene raccolto per filtrazione, lavato con acqua e asciugato sotto vuoto a 40°C. Si ottengono 8,5 g del prodotto desiderato.

$C_{14}H_9NO_3$

P.M. - 239,23

DESCRIZIONE 7

2-(2-furil)-4-chinolincarbonil cloruro

5,2 ml (60,4 mmoli) di ossalil cloruro vengono sciolti in 70 ml di CH_2Cl_2. La soluzione viene raffreddata a -10°C e vengono aggiunti, in più' porzioni, 8,5 g (35,5 mmoli) di acido 2-(2-furil)-4-chinolincarbossilico. La miscela di reazione viene lasciata a se', a temperatura ambiente, per tutta la notte e poi evaporata a secco sotto vuoto. Si ottengono 9,2 g del prodotto desiderato, utilizzato senza ulteriori purificazioni.

$C_{14}H_8ClNO_2$

P.M. - 257,78

DESCRIZIONE 8

acido 2-(4-piridil)-4-chinolincarbossilico cloridrato

5 g (34,0 mmoli) di isatina, 4,5 ml (40,8 mmoli) di 4-acetilpiridina e 6,3 g (112,2 mmoli) di idrossido di potassio vengono sciolti in 40 ml di EtOH assoluto e la sospensione viene scaldata a 80°C per 12 ore. La miscela di reazione viene raffreddata, vengono aggiunti 50 ml di acqua e la soluzione viene estratta con 50 ml di Et_2O. La fase acquosa, raffreddata con ghiaccio, viene acidificata a pH 1 con HCl al 37% e il precipitato viene raccolto per filtrazione e lavato con acqua. La soluzione acquosa viene evaporata a secco sotto vuoto, il residuo viene triturato con EtOH e filtrato via. L'evaporazione del solvente fornisce 6,0 g di grezzo che, unito al precipitato ottenuto in precedenza, viene ricristallizzato da toluene contenente tracce di MeOH. Si ottengono 4,5 g del prodotto desiderato.

$C_{15}H_{10}N_2O_2.HCl$

P.F. = 297-301°C

P.M. = 286,72

I.R. (KBr): 1705; 1635; 1610 cm-1.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 8,90 (d, 2H); 8,70 (m, 2H); 8,50 (s, 2H); 8,28 (d, 1H); 7,89 (dt, 2H).

DESCRIZIONE 9

2-(4-piridil)-4-chinolincarbonil cloruro cloridrato

1,3 ml (10,4 mmoli) di ossalil cloruro vengono sciolti in 60 ml di CH_2Cl_2. La soluzione viene raffreddata a -10°C e vengono aggiunti, in più' porzioni, 3,0 g (14,4 mmoli) di acido 2-(4-piridil)-4-chinolincarbossilico cloridrato. La miscela di reazione viene lasciata a se', a temperatura ambiente, per 72 ore e poi evaporata a secco sotto vuoto. Si ottengono 4,0 g del prodotto desiderato, utilizzato senza ulteriori purificazioni.

$C_{15}H_9ClN_2O \cdot HCl$

P.M. = 305,22

ESEMPIO 1

(R,S)-N-(α-metilbenzil)-2-fenilchinolina-4-carbossammide

1,2 ml (9,4 mmoli) di (R,S) α-metilbenzilammina e 1,6 ml (11,7 mmoli) di trietilammina (TEA) vengono sciolti, sotto azoto, in 50 ml di una miscela 1:1 di CH_2Cl_2 anidro e CH_3CN. 2,0 g (7,8 mmoli) di 2-fenil-4-chinolincarbonil cloruro, sciolti in 50 ml di una miscela 1:4 di CH_2Cl_2 anidro e DMF, vengono gocciolati nella soluzione dell'ammina, raffreddata con un bagno di ghiaccio. La reazione viene mantenuta per 1

ora tra 0° e 5°C e poi a temperatura ambiente per tutta la notte. La miscela di reazione viene evaporata a secco sotto vuoto ed il residuo viene sciolto in AcOEt e lavato due volte con una soluzione satura di $NaHCO_3$. La fase organica viene separata, seccata su Na_2SO_4, filtrata ed evaporata a secco sotto vuoto.

L'olio residuo viene cristallizzato da AcOEt per fornire 1,1 g del prodotto desiderato.

$C_{24}H_{20}N_2O$

P.F. - 156-157C

P.M. - 352,43

Analisi elementare:

Calcolato: C, 81,79; H, 5,72; N, 7,95;

Trovato: C, 81,99; H, 5,69; N, 7,89.

I.R. (KBr): 3240;1645 cm^{-1}.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 9,29 (d, 1H); 8,32 (d, 2H); 8,13 (d, 1H); 8,13 (s, 1H); 8,06 (d, 1H); 7,81 (ddd, 1H); 7,68-7,52 (m, 4H); 7,47 (d, 2H); 7,39 (dd, 2H); 7,27 (dd, 1H); 5,30 (dq, 1H); 1,52 (d, 3H).

MS (EI; source 200 C; 70 V; 200 mA): 352 (M+.); 337; 232; 204; 77.

ESEMPIO 2

S-(+)-N-(α-metilbenzil)-2-fenilchinolina-4-carbossammide

Preparata come descritto nell'Esempio 1 partendo da 1,2 ml (9,4 mmoli) di S-(-)-α-metilbenzilammina, 1,6 ml (11,7 mmoli) di TEA, 2,0 g (7,8 mmoli) di 2-fenil-4-chinolincarbonil cloruro in 100 ml di una miscela di CH_2Cl_2, CH_3CN e DMF. La miscela di reazione viene lavorata come descritto nell'Esempio 1. L'olio residuo viene cristallizzato da

AcOEt per fornire 1,1 g del prodotto desiderato.

$C_{24}H_{20}N_2O$

P.F. - 161-162C

P.M. - 352,43

$[\ ]_D^{20}$ = + 25 (C = 0,5, DMF)

I.R. (KBr): 3240; 1645 cm^{-1}.

300 MHz ^1H-NMR (DMSO-d_6): δ 9,29 (d, 1H); 8,32 (d, 2H); 8,13 (d, 1H); 8,13 (s, 1H); 8,06 (d, 1H); 7,81 (ddd, 1H); 7,68-7,52 (m, 4H); 7,47 (d, 2H); 7,39 (dd, 2H); 7,27 (dd, 1H); 5,30 (dq, 1H); 1,52 (d, 3H).

Lo spettro di massa è identico a quello dell'Esempio 1.

ESEMPIO 3

R-(-)-N-(α-metilbenzil)-2-fenilchinolina-4-carbossammide

Preparata come descritto nell'Esempio 1 partendo da 1,2 ml (9,4 mmoli) di R-(+)-α-metilbenzilammina 1,6 ml (11,7 mmoli) di TEA, 2,0 g (7,8 mmoli) di 2-fenil-4-chinolincarbonil cloruro in 100 ml di una miscela di CH_2Cl_2, CH_3CN e DMF.

La miscela di reazione viene lavorata come descritto nell'Esempio 1. L'olio residuo viene cristallizzato da AcOEt per fornire 1,1 g del prodotto desiderato.

$C_{24}H_{20}N_2O$

P.F. - 158-160C

P.M. - 352,43

$[\alpha]_D^{20}$ - -25 (C - 0,5, DMF)

I.R. (KBr): 3240; 1645 cm^{-1}.

^1H-NMR e spettro di massa sono identici a quelli degli Esempi 1 e 2.

ESEMPIO 4

(R,S)-N-[α-(metossicarbonil)benzil]-2-fenilchinolina-4-carbossammide

2,0 g (8,0 mmoli) di acido 2-fenil-4-chinolincarbossilico vengono sciolti, sotto azoto, in 130 ml di THF anidro e 100 ml di CH_3CN. Si aggiungono 2,0 g (9,9 mmoli) di cloridrato dell'estere metilico della (D,L) fenilglicina e 1,5 ml (10,7 mmoli) di TEA e la miscela di reazione viene raffreddata a 5°C.

Si gocciolano 2,5 g (12,1 mmoli) di dicicloesilcarbodiimmide (DCC), sciolti in 10 ml di CH_2Cl_2 anidro, e la reazione viene lasciata rinvenire a temperatura ambiente e a se' per tutta la notte.

La dicicloesilurea che precipita viene filtrata via e la soluzione evaporata a secco sotto vuoto. Il residuo viene sciolto in CH_2Cl_2 e lavato con acqua. La fase organica separata viene seccata su Na_2SO_4 ed evaporata a secco sotto vuoto per ottenere 6,0 g di prodotto grezzo che viene sciolto in 20 ml di CH_2Cl_2 e lasciato a se' per tutta la notte. Precipita dell'altra dicicloesilurea che viene filtrata via.

La soluzione viene evaporata a secco sotto vuoto ed il residuo flash cromatografato su gel di silice (230-400 mesh) usando come eluente una miscela di esano/AcOEt 3:2 contenente lo 0,5% di NH_4OH (al 28%). Il prodotto ottenuto viene triturato a caldo con i-Pr_2O, filtrato, lavato e seccato per fornire 1,1 g del prodotto desiderato.

$C_{25}H_{20}N_2O_3$

P.F. - 170-172°C

P.M. - 396,45

Analisi elementare:

Calcolato: C, 75,74; H, 5,09; N, 7,07;

Trovato: C, 75,88; H, 5,12; N, 7,06.

I.R. (nujol): 3240; 1750; 1670 cm^{-1}.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 9,72 (d, 1H); 8,28 (dd, 2H); 8,20 (dd, 1H); 8,13 (dd, 1H); 8,11 (s, 1H); 7,83 (ddd, 1H); 7,66 (ddd, 1H); 7,60-7,50 (m, 5H); 7,47-7,37 (m, 3H); 5,78 (d, 1H); 3,72 (s, 3H).

MS (EI; source 200 °C; 70 V; 200 mA): 396 (M+.); 337; 232; 204.

ESEMPIO 5

(+)-(S)-N-[α(metossicarbonil)benzil]-2-fenilchinolina-4-carbossammide

2,0 g (8,0 mmoli) di acido 2-fenil-4-chinolincarbossilico vengono sciolti, sotto azoto, in 70 ml di THF anidro e 30 ml di CH_3CN.

Si aggiungono 1,7 g (8,4 mmoli) di cloridrato dell'estere metilico della (L) fenilglicina, 1,1 ml (9,9 mmoli) di N-metilmorfolina e 2,1 g (15,5 mmoli) di N-idrossibenzotriazolo (HOBT) e la miscela di reazione viene raffreddata a 0°C. Si gocciolano 1,85 g (9,0 mmoli) di DCC, sciolti in 10 ml di CH_2Cl_2 anidro, e la reazione viene poi tenuta tra 0° e 5°C per 1 ora e a temperatura ambiente per 2 ore. La dicicloesilurea che precipita viene filtrata via e la soluzione viene evaporata a secco sotto vuoto. Il residuo viene sciolto in CH_2Cl_2 e lavato con acqua, $NaHCO_3$ sol. sat., acido citrico al 5%, $NaHCO_3$ sol. sat. e NaCl sol. sat..

La fase organica separata viene seccata su Na_2SO_4 ed evaporata a secco sotto vuoto; il residuo viene sciolto in 20 ml di CH_2Cl_2 e lasciato a se' per tutta la notte. Precipita dell'altra dicicloesilurea

che viene filtrata via.

La soluzione viene evaporata a secco sotto vuoto per ottenere 2,6 g di prodotto grezzo che viene triturato con etere di petrolio, filtrato, lavato con i-Pr_2O e ricristallizzato con 70 ml di i-PrOH per ottenere 1,7 g del prodotto desiderato.

$C_{25}H_{20}N_2O_3$

P.F. - 180-181°C

P.M. - 396,45

I.R. (nujol): 3300; 1750; 1640 cm^{-1}.

$_D^{20}$ = +42,0 (C = 0,5, MeOH).

^{1}H-NMR e spettro di massa sono identici a quelli dell'Esempio 4.

ESEMPIO 6

(-)-(R)-N-[α-(metossicarbonil)benzil]-2-fenilchinolina-4-carbossammide

Preparata come descritto nell'Esempio 5 da 2,0 g (8,0 mmoli) di acido 2-fenil-4-chinolincarbossilico, 1,7 g (8,4 mmoli) di cloridrato dell'estere metilico della (D) fenilglicina, 1,1 ml (9,9 mmoli) di N-metilmorfolina, 2,1 g (15,5 mmoli) di HOBT e 1,85 g (9,0 mmoli) di DCC in 70 ml di THF anidro e 30 ml di CH_3CN.

La miscela di reazione viene lavorata come descritto nell'Esempio 5. Il prodotto grezzo ottenuto (3,5 g) viene triturato a caldo due volte con i-Pr_2O, filtrato, lavato e ricristallizzato con 80 ml di i-PrOH per ottenere 2,3 g del prodotto desiderato.

$C_{25}H_{20}N_2O_3$

P.F. - 180-181°C

P.M. - 396,45

I.R. (nujol): 3300; 1750; 1640 cm^{-1}.

$[\alpha]_D^{20}$ = -42,0 (C = 0,5, MeOH).

^{1}H-NMR e spettro di massa sono identici a quelli degli Esempi 4 e 5.

ESEMPIO 7

(R,S)-N-[α-(metossicarbonil)benzil]-2-fenil-7-metossichinolina-4-carbossammide

1,0 g (5,0 mmoli) di cloridrato dell'estere metilico della (D,L) fenilglicina vengono sciolti, sotto azoto, in 30 ml di DMF anidra. Si aggiungono 2,5 g (18,1 mmoli) di carbonato di potassio anidro e la soluzione viene raffreddata a 0°C. Si gocciolano 0,7 g (2,3 mmoli) del prodotto della Descrizione 3, sciolti in 25 ml di DMF anidra, e la reazione viene mantenuta tra 0° e 5°C per 1 ora e a temperatura ambiente per tutta la notte.

La miscela di reazione viene evaporata a secco sotto vuoto e il residuo viene sciolto in AcOEt e lavato due volte con acqua. La fase organica separata viene seccata su Na_2SO_4, filtrata ed evaporata a secco sotto vuoto.

L'olio residuo viene flash cromatografato su gel di silice (230-400 mesh) usando come eluente una miscela di esano/AcOEt 3:2 contenente lo 0,5% di NH_4OH (al 28%), per ottenere 0,1 g di prodotto grezzo che viene triturato con i-Pr_2O. Si ottengono 0,08 g del prodotto desiderato.

$C_{26}H_{22}N_2O_4$

P.F. - 187-190°C

P.M. - 426,48

I.R. (KBr): 3220; 1750; 1660; 1620 cm^{-1}.

300 MHz ^1H-NMR ($CDCl_3$): δ 8,13-8,08 (m, 3H); 7,80 (s, 1H); 7,55-7,38 (m, 9H); 7,21 (dd, 1H); 7,02 (d broad, 1H); 5,88 (d, 1H); 3,97 (s, 3H); 3,80 (s, 3H).

MS (EI; source 200 °C; 70 V; 200 mA): 426 (M+.); 367 ; 262 ; 234; 191; 77.

ESEMPIO 8

(R,S)-N-[α-(metossicarbonil)benzil]-2-fenil-7-idrossichinolina-4-carbossammide

Preparata come descritto nell'Esempio 5 da 2,1 g (5,3 mmoli) del prodotto della Descrizione 4, 1,08 g (5,3 mmoli) di cloridrato dell'estere metilico della (D,L) fenilglicina, 1,5 ml (10,7 mmoli) di TEA, 1,7 g (12,5 mmoli) di HOBT e 1,2 g (5,8 mmoli) di DCC in 70 ml di THF anidro e 30 ml di CH_3CN.

La miscela di reazione viene lavorata come descritto nell'Esempio 5. Il prodotto grezzo ottenuto viene triturato con $i\text{-}Pr_2O$ e ricristallizzato due volte da i-PrOH per ottenere 0,06 g del prodotto desiderato.

$C_{25}H_{20}N_2O_4$

P.F. - 256-257°C

P.M. - 412,45

I.R. (KBr): 3270; 1750; 1650; 1620 cm^{-1}.

300 MHz ^1H-NMR (DMSO-d_6): δ 10,30 (s broad, 1H); 9,64 (d, 1H); 8,22 (d, 2H); 8,04 (d, 1H); 7,85 (s, 1H); 7,60-7,34 (m, 9H); 7,21 (dd, 1H); 5,74 (d, 1H); 3,71 (s, 3H).

MS (EI; source 200 °C; 70 V; 200 mA): 412 (M+.); 353; 248; 220; 77.

ESEMPIO 9

(R,S)-N-[α-(carbossi)benzil]-2-fenil-7-metossichinolina-4-carbossammide cloridrato

0,18 g (0,4 mmoli) del prodotto dell'Esempio 7 vengono sciolti in 10 ml di HCl al 10% e 5 ml di diossano. La miscela di reazione viene scaldata a ricadere sotto agitazione magnetica per 3 ore e poi evaporata a secco sotto vuoto.

Il prodotto grezzo viene triturato a caldo con AcOEt (contenente qualche goccia di EtOH) per fornire 0,16 g del prodotto desiderato.

$C_{25}H_{20}N_2O_4 \cdot HCl$

P.F. - 228-230°C

P.M. - 448,91

I.R. (KBr): 3180; 1735; 1655; 1630 cm^{-1}.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 9,6 (d, 1H); 8,26 (dd, 2H); 8,14 (d, 1H); 7,98 (s, 1H); 7,63-7,52 (m, 6H); 7,46-7,36 (m, 3H); 7,33 (dd, 1H); 5,66 (d, 1H); 3,98 (s, 3H).

MS (EI; source 200 °C; 70 V; 200 mA): 412 (M+.); 368 ; 262; 234; 191; 77.

ESEMPIO 10

(R,S)-N-[α-(metilamminocarbonil)benzil]2-fenilchinolina-4-carbossammide

0,45 g (1,1 mmoli) del prodotto dell'Esempio 4 vengono sciolti in 40 ml di $MeNH_2$/EtOH al 33%; dopo l'aggiunta di una quantità catalitica di NaCN la miscela di reazione viene scaldata a 70°C per 1 ora in un apparato di Parr. La pressione interna sale a 40 psi.

La soluzione viene quindi evaporata a secco sotto vuoto ed il residuo viene triturato con acqua, filtrato, seccato e ricristallizzato con una miscela di i-PrOH (50 ml) e EtOH (30 ml) per ottenere 0,2 g del prodotto desiderato.

$C_{25}H_{21}N_3O_2$

P.F. - 261-263°C

P.M. - 395,47

Analisi elementare:

Calcolato: C, 75,93; H, 5,35; N, 10,63;

Trovato: C, 75,65; H, 5,34; N, 10,55.

I.R. (KBr): 3300; 3270; 1660; 1635 cm^{-1}.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 9,48 (d, 1H); 8,33-8,25 (m, 3H); 8,18-8,10 (m, 3H); 7,80 (ddd, 1H); 7,68-7,50 (m, 6H); 7,40-7,28 (m, 3H); 5,75 (d, 1H); 2,63 (d, 3H).

MS (EI; source 200 °C; 70 V; 200 mA): 395 (M+.); 337; 232; 204; 77.

ESEMPIO 11

(R,S)-N-[α(metossicarbonil)benzil]-2-(2-tienil)chinolina-4-carbossammide

Preparata come descritto nell'Esempio 5 da 2,0 g (7,3 mmoli) di acido 2-(2-tienil)-4-chinolincarbossilico, 1,7 g (8,4 mmoli) di cloridrato dell'estere metilico della (D,L) fenilglicina, 1,1 ml (10 mmoli) di N-metilmorfolina, 2,1 g (15,5 mmoli) di HOBT e 1,85 g (9,0 mmoli) di DCC in 70 ml di THF anidro e 30 ml di CH_3CN.

La miscela di reazione viene lavorata come descritto nell'Esempio 5. Il prodotto grezzo ottenuto viene cristallizzato da AcOEt e poi

ricristallizzato da EtOH assoluto per ottenere 0,9 g del prodotto desiderato.

$C_{23}H_{18}N_2O_3S$

P.F. - 178-180°C

P.M. - 402,47

Analisi elementare:

Calcolato: C, 68,64; H, 4,51; N, 6,96;

Trovato: C, 67,50; H, 4,99; N, 7,43.

I.R. (KBr): 3300; 1745; 1645 cm^{-1}.

300 MHz ^1H-NMR (DMSO-d_6): δ 9,70 (d, 1H); 8,12 (d, 1H); 8,08 (s, 1H); 8,04 (d, 1H); 8,02 (d, 1H); 7,19 (t, 1H); 7,76 (d, 1H); 7,62 (t, 1H); 7,53 (d, 2H); 7,46-7,37 (m, 3H); 7,30 (dd, 1H); 5,68 (d, 1H); 3,68 (s, 3H).

MS (EI; source 200 °C; 70 V; 200 mA): 402 (M+.); 343; 238; 210; 77.

ESEMPIO 12

(R,S)-N-[α-(metossicarbonil)benzil]-2-(2-furil)chinolina-4-carbossammide

Preparata come descritto nell'Esempio 1 da 7,2 g (35,5 mmoli) di cloridrato dell'estere metilico della (D,L) fenilglicina, 12,4 ml (88,8 mmoli) di TEA e 9,1 g (35,5 mmoli) di 2-(2-furil)-4-chinolincarbonil cloruro in 350 ml di una miscela di CH_2Cl_2, CH_3CN e DMF. La miscela di reazione viene lavorata come descritto nell'Esempio 1. Il prodotto grezzo viene triturato con MeOH per fornire 3,3 g del prodotto desiderato.

$C_{23}H_{18}N_2O_4$

P.F. - 178-180°C

P.M. - 386,40

Analisi elementare:

Calcolato: C, 71,49; H, 4,70; N, 7,25;

Trovato: C, 71,67; H, 4,74; N, 7,17.

I.R. (KBr): 3300; 1750; 1650 cm^{-1}.

300 MHz ^1H-NMR ($DMSO-d_6$): δ 9,72 (d, 1H); 8,12 (d, 1H); 8,06 (d, 1H); 7,96 (dd, 1H); 7,92 (s, 1H); 7,80 (ddd, 1H); 7,62 (ddd, 1H); 7,52 (dd, 2H); 7,45-7,35 (m, 4H); 6,73 (dd, 1H); 5,77 (d, 1H); 3,74 (s, 3H).

MS (EI; source 200 °C; 70 V; 200 mA): 386 (M+.); 327; 222; 194; 77.

ESEMPIO 13

(R,S)-N-[α-(metossicarbonil)benzil]-2-(4-piridil)chinolina-4-carbossammide

Preparata come descritto nell'Esempio 1 da 3,4 g (16,7 mmoli) di cloridrato dell'estere metilico della (D,L) fenilglicina, 3,9 ml (27,8 mmoli) di TEA e 3,0 g (11,1 mmoli) di 2-(4-piridil)-4-chinolincarbonil cloruro in 100 ml di una miscela di CH_2Cl_2, CH_3CN e DMF. La miscela di reazione viene lavorata come descritto nell'Esempio 1. Il prodotto grezzo viene ricristallizzato tre volte da AcOEt per fornire 1,9 g del prodotto desiderato.

$C_{24}H_{19}N_3O_3$

P.F. - 172-174°C

P.M. - 397,43

Analisi elementare:

Calcolato: C, 72,53; H, 4,82; N, 10,57;

Trovato: C, 71,87; H, 4,87; N, 10,44.

I.R. (KBr): 3240; 1750; 1670 cm^{-1}.

300 MHz ^1H-NMR (DMSO-d_6): δ 9,74 (d, 1H); 8,79 (dd, 2H); 8,27-8,17 (m, 5H); 7,89 (ddd, 1H); 7,74 (ddd, 1H); 7,54 (dd, 2H); 7,47-7,38 (m, 3H); 5,80 (d, 1H); 3,75 (s, 3H).

MS (EI; source 200 °C; 70 V; 200 mA): 397 (M+.); 338; 233; 205; 77.

ESEMPIO 14

(R,S)-N-[α-(metossicarbonil)-2-tienilmetil]-2-fenilchinolina-4-carbossammide

Preparata come descritto nell'Esempio 1 da 1,94 g (9,4 mmoli) di cloridrato dell'estere metilico della (D,L) tienilglicina, 2,7 ml (19,5 mmoli) di TEA e 2,0 g (7,8 mmoli) di 2-fenil-4-chinolincarbonil cloruro in 100 ml di una miscela di CH_2Cl_2, CH_3CN e DMF. La miscela di reazione viene lavorata come descritto nell'Esempio 1. Il prodotto grezzo viene ricristallizzato tre volte da AcOEt per fornire 0,66 g del prodotto desiderato.

$C_{23}H_{18}N_2O_3S$

P.F. - 144-145°C

P.M. - 402,47

Analisi elementare:

Calcolato: C, 68,64; H, 4,51; N, 6,96;

Trovato: C, 68,81; H, 4,46; N, 6,96.

I.R. (KBr): 3295; 1745; 1640 cm^{-1}.

300 MHz ^1H-NMR ($CDCl_3$): δ 8,25 (dd, 1H); 8,22 (dd, 1H); 8,17 (dd, 2H); 7,95 (s, 1H); 7,78 (ddd, 1H); 7,60 (ddd, 1H); 7,56-7,45 (m, 3H); 7,35

(dd, 1H) ; 7,20 (d, 1H); 7,05 (dd, 1H); 7,05 (s broad, 1H); 6,22 (d, 1H); 3,90 (s, 3H).

MS (EI; source 200 °C; 70 V; 200 mA): 402 (M+.); 343; 232; 204.

ESEMPIO 15

(R,S)-N-[α-(metossicarbonilmetil)benzil]-2-fenilchinolina-4-carbossammide

Preparata come descritto nell'Esempio 5 da 1,39 g (5,6 mmoli) di acido 2-fenil-4-chinolincarbossilico, 1,2 g (5,6 mmoli) di cloridrato dell' (R,S) 3-ammino-3-fenilproprionato di metile, 0,78 ml (5,6 mmoli) di TEA, 1,51 g (11,2 mmoli) di HOBT e 2,31 g (11,2 mmoli) di DCC in 10 ml di THF anidro, 4 ml di CH_3CN e 7 ml di CH_2Cl_2. La miscela di reazione viene lavorata come descritto nell'Esempio 5. Il prodotto grezzo viene sciolto in CH_2Cl_2 e lasciato a 0°C per tutta la notte. La dicicloesilurea che precipita viene filtrata via. La soluzione viene evaporata a secco sotto vuoto per ottenere 1,4 g di prodotto grezzo che viene triturato con una miscela di i-Pr_2O/acetone 99:1. Si ottengono 1,2 g del prodotto desiderato.

$C_{26}H_{22}N_2O_3$

P.F. - 156-158°C

P.M. = 410,47

Analisi elementare:

Calcolato: C, 76,07; H, 5,40; N, 6,82;

Trovato: C, 75,77; H, 5,38; N, 6,94.

I.R. (KBr): 3295; 1755; 1645 cm^{-1}.

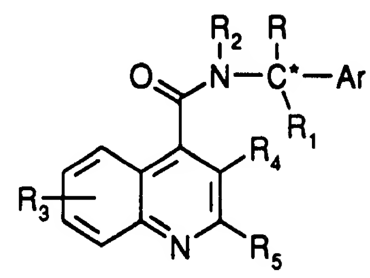
300 MHz ^1H-NMR (DMSO-d_6): δ 9,40 (d, 1H); 8,29 (dd, 2H); 8,14 (d, 1H);

8,07 (d, 1H); 8,04 (s, 1H); 7,83 (ddd, 1H); 7,66-7,52 (m, 4H); 7,50 (d, 2H); 7,40 (dd, 2H); 7,31 (ddd, 1H); 5,60 (dt, 1H); 3,65 (s, 3H); 3,04-2,89 (m, 2H).

MS (EI; source 200 °C; 70 V; 200 mA): 410 (M+.); 337; 233; 205.

Le caratteristiche dei composti degli Esempi sono riportate nella Tabella seguente.

TABELLA



Es.	Ar	R	R_1	R_2	R_3	R_4	R_5	*	Formula Molecolare	P.F. °C	$[\alpha]_D^{20}$ c=0.5,MeOH
1	Ph	Me	H	H	H	H	Ph	(R,S)	$C_{24}H_{20}N_2O$	156-157	
2	Ph	Me	H	H	H	H	Ph	(S)	$C_{24}H_{20}N_2O$	161-162	+25° a
3	Ph	Me	H	H	H	H	Ph	(R)	$C_{24}H_{20}N_2O$	158-160	-25° a
4	Ph	COOMe	H	H	H	H	Ph	(R,S)	$C_{25}H_{20}N_2O_3$	170-172	
5	Ph	COOMe	H	H	H	H	Ph	(S)	$C_{25}H_{20}N_2O_3$	180-181	+42°
6	Ph	COOMe	H	H	H	H	Ph	(R)	$C_{25}H_{20}N_2O_3$	180-181	-42°
7	Ph	COOMe	H	H	7-OMe	H	Ph	(R,S)	$C_{26}H_{22}N_2O_4$	187-190	
8	Ph	COOMe	H	H	7-OH	H	Ph	(R,S)	$C_{25}H_{20}N_2O_4$	256-257	
9	Ph	COOH	H	H	7-OMe	H	Ph	(R,S)	$C_{25}H_{20}N_2O_4$.HCl	228-230	
10	Ph	CONHMe	H	H	H	H	Ph	(R,S)	$C_{25}H_{21}N_3O_2$	261-263	
11	Ph	COOMe	H	H	H	H	2-tienil	(R,S)	$C_{23}H_{18}N_2O_3S$	178-180	
12	Ph	COOMe	H	H	H	H	2-furil	(R,S)	$C_{23}H_{18}N_2O_4$	178-180	
13	Ph	COOMe	H	H	H	H	4-piridil	(R,S)	$C_{24}H_{19}N_3O_3$	172-174	
14	2-tienil	COOMe	H	H	H	H	Ph	(R,S)	$C_{23}H_{18}N_2O_3S$	144-145	
15	Ph	CH_2COOMe	H	H	H	H	Ph	(R,S)	$C_{26}H_{22}N_2O_3$	156-158	

a solvente DMF

Seguendo la procedura descritta negli Esempi precedenti, sono stati preparati i composti che compaiono nell'elenco seguente.

1) N-[α-(metossicarbonil)benzil]-2-cicloesilchinolin-4-carbossammide;

2) N-[α-(metossicarbonil)benzil]-2-(o-clorofenil)chinolin-4-carbossammide;

3) N-[α-(metossicarbonil)benzil]-2-(m-clorofenil)chinolin-4-carbossammide;

4) N-[α-(metossicarbonil)benzil]-2-(p-clorofenil)chinolin-4-carbossammide;

5) (R)-N-[α-(metossicarbonil)-4-idrossibenzil]-2-fenilchinolin-4-carbossammide;

6) N-[α-(idrossimetil)benzil]-2-fenilchinolin-4-carbossammide;

7) N-[α-(amminocarbonil)benzil]-2-fenilchinolin-4-carbossammide;

8) N-[α-(dimetilamminocarbonil)benzil]-2-fenilchinolin-4-carbossammide;

9) N-[α-(metossicarbonil)benzil]-N-metil-2-fenilchinolin-4-carbossammide;

10) N-[α-(metossicarbonil)benzil]-3-metil-2-fenilchinolin-4-carbossammide;

11) N-[α-(metossicarbonil)benzil]-6-fluoro-2-fenilchinolin-4-carbossammide;

12) N-[α-(metossicarbonil)benzil]-6-metossi-2-fenilchinolin-4-carbossammide;

13) N-[α-(metossicarbonil)benzil]-6-metil-2-fenilchinolin-4-carbossammide;

14) N-[α-(etil)benzil]-2-fenilchinolin-4-carbossammide;

15) N-[α-(metossicarbonil)-α-(metil)benzil]-N-metil-2-fenilchinolin-4-carbossammide;

16) N-[α-(metossicarbonil)benzil]-2-(3-tienil)chinolin-4-carbossammide;

17) N-[α-(metossicarbonil)benzil]-2-(2-pirril)chinolin-4-carbossammide;

18) N-[α-(metossicarbonil)benzil]-2-(2-tiazolil)chinolin-4-carbossammide;

19) N-[α-(metossicarbonil)benzil]-6-cloro-2-fenilchinolin-4-carbossammide;

20) N-[α-(metossicarbonil)benzil]-7-cloro-2-fenilchinolin-4-carbossammide;

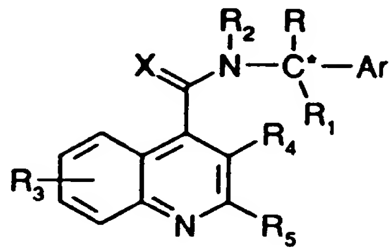
21) N-[α-(metilcarbonil)benzil]-2-fenilchinolin-4-carbossammide;

22) N-[α-(amminometil)benzil]-2-fenilchinolin-4-carbossammide;

23) N-[α-(trifluorometil)benzil]-2-fenilchinolin-4-carbossammide.

RIVENDICAZIONE

Composti di formula (I)



(I)

in cui:

Ar è un fenile o naftile eventualmente sostituito o un gruppo eterociclico ad anello singolo o fuso, eventualmente sostituito, di carattere aromatico, contenente da 5 a 12 atomi d'anello e comprendente fino a quattro eteroatomi nell'anello o in ciascun anello, scelti tra S, O, N; con la condizione che Ar non sia p-isobutilfenile; R è C_{1-6} alchile lineare o ramificato, C_{3-7} cicloalchile, C_{4-7} cicloalchilalchile, fenile eventualmente sostituito, anelli eteroaromatici eventualmente sostituiti a 5-elementi, comprendenti fino a quattro eteroatomi scelti tra O o N, idrossi C_{1-6} alchile, ammino C_{1-6} alchile, C_{1-6} alchilamminoalchile, di C_{1-6} alchilamminoalchile, C_{1-6} acilamminoalchile, C_{1-6} alcossialchile, C_{1-6} alchilcarbonile, carbossi, C_{1-6} alcossicarbonile, amminocarbonile, C_{1-6} alchilamminocarbonile, di C_{1-6} alchilamminocarbonile, alogeno C_{1-6} alchile;

R_1 e R_2, che possono essere uguali o diversi, sono indipendentemente idrogeno o C_{1-6} alchile lineare o ramificato, oppure insieme formano un gruppo $-(CH_2)_n-$ in cui n rappresenta 3, 4 o 5;

R_3 e R_4, che possono essere uguali o diversi, sono indipendentemente idrogeno, C_{1-6} alchile lineare o ramificato, C1-6 alchenile, arile, C1-6

alcossi, idrossi, alogeno, nitro, ciano, carbossi, carbossammido, solfonammido, C_{1-6} alcossicarbonile o trifluorometile, con fino a quattro sostituenti R_3 nel nucleo chinolinico;

R_5 è C_{1-6} alchile lineare o ramificato, C_{3-7} cicloalchile, C_4-C_7 cicloalchilalchile, arile eventualmente sostituito, o un gruppo eterociclico ad anello singolo o fuso, eventualmente sostituito, di carattere aromatico, contenente da 5 a 12 atomi nell'anello e comprendente fino a quattro eteroatomi nell'anello o in ciascun anello, scelti tra S, O, N; X è O, S o N-C≡N.

Milano, 27 maggio 1994

Il Mandatario
(Minoja Fabrizio)
dello Studio Consulenza Brevettuale s.r.l.

Fabrizio Minoja

MINISTRY OF INDUSTRY, TRADE AND HANDICRAFT
GENERAL DIRECTORATE OF INDUSTRIAL PRODUCTION
CENTRAL PATENT OFFICE

One £. 15,000.- revenue stamp and seal of the Ministry of Industry, Trade and Handicraft. Central Patent Office.

Certification of copy of documents relating to a patent application for industrial invention N. MI95A000494

It is hereby declared that the enclosed copy corresponds to the documents as originally filed with the above mentioned patent application whose data are as from the enclosed filing certificate.

Rome, 14 April 1995

THE DIRECTOR OF THE DIVISION
The first director
Dr Giuseppe PETRUCCI
(signature)

WHITE, RED AND GREEN RIBBON AND ORANGE SEAL OF THE MINISTRY OF INDUSTRY, TRADE AND HANDICRAFT.
CENTRAL PATENT OFFICE

TO THE MINISTRY OF INDUSTRY, TRADE AND HANDICRAFT
CENTRAL PATENT OFFICE - ROME

Space to be covered with stamps
FORM A

APPLICATION FOR INDUSTRIAL INVENTION, FILING MISSING DOCUMENTS, ADVANCED AVAILABILITY TO THE PUBLIC

A. APPLICANT(S)

1) NAME SmithKline Beecham Farmaceutici S.p.A. J.N. [SP]
RESIDING IN Baranzate di Bollate (Milan) CODE 03524320151
2) NAME [ ]
RESIDING IN CODE

B. APPLICANT'S REPRESENTATIVE AT THE CENTRAL PATENT OFFICE
SURNAME, NAME: BIANCHETTI, Giuseppe et al FISCAL CODE:
NAME OF THE OFFICE: STUDIO CONSULENZA BREVETTUALE S.r.l.
STREET: Rossini N. 8 TOWN: MILAN ZIP CODE: 20122 PROV.: MI

C. ADDRESSEE'S ELECTIVE DOMICILE:
STREET: N. TOWN: ZIP CODE: PROV:

D. TITLE proposed class(sect/cl/scl):[C07D] group/sub-group:[215/00

"Quinoline derivatives"

ADVANCED ACCESS TO THE PUBLIC: YES[ ] NO[X]
IF REQUEST: DATE / / / RECORD N. [ ]

E. NAMED INVENTORS:

	surname, name		surname, name
1)	FARINA, Carlo	3)	GRUGNI, Mario
2)	GIARDINA, Giuseppe	4)	RAVEGLIA, Luca

F. PRIORITY

COUNTRY OR ORGANIZATION	KIND OF PRIORITY	APPL.N.	FILING DATE	ENCL Y/M
1)			/ /	
2)			/ /	

MISSING DOCUMENTS FILED: FILING DATE DOCUMENT N.
1) / /
2) / /

G. AUTHORIZED COLLECTING CENTER FOR MICROORGANISMS CULTURE
Name:

H. SPECIAL NOTES:

ENCLOSED DOCUMENTS:
N. COPIES

DOC. 1) [01] [PROV] N.PAGES [85] abstract and main drawing, description and claims (1 copy compulsory)

DOC. 2) [00] [PROV] N.SHEET [ ] OF DRAWING drawing (1 copy compulsory if cited in the description)

DOC. 3) [01] [FOLLOWS power of attorney

DOC. 4) [01] [FOLLOWS] designation of inventor

DOC. 5) [00] [FOLLOW] priority documents with Italian translation

DOC. 6) [00] [FOLLOWS] authorization or assignment act

DOC. 7) [00] full name of the applicant

MISSING DOCUMENTS FILED:

DATE RECORD N.

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compare single priorities

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8. Payment receipts, Total amount Lira NINE HUNDRED AND EIFTEEN THOUSAND compulsory

9. Revenue stamps for letters patent Lira compulsory

FILLED IN ON 14/03/1995 SIGNATURE OF THE APPLICANT(S)

CONTINUES YES/NO [NO] BRACCO, Mauro

CERTIFIED COPY OF THE PRESENT ACT IS REQUESTED YES/NO [YES]

PROVINCIAL OFFICE IND. TRADE HAND. OF MILAN CODE [15]

FILING CERTIFICATE: APPLICATION NUMBER MI95/A 000494 Reg.A

The year NINETEEN NINETY FIVE, this FOURTEENTH day of the month of MARCH the above mentioned applicant(s) has(have) produced to me the undersigned the present application, consisting of N. [00] additional sheets for the granting of the overmentioned patent.

I. VARIOUS NOTES OF THE ATTESTING OFFICER

THE PETITIONER	SEAL OF THE OFFICE	THE ATTESTING OFFICER
(signature)	Seal of the Ministry of Industry, Commerce and Handicraft One £. 15,000.- revenue stamp.	CORTONESI Maurizio (signature)

One £. 15,000.- revenue stamp
Seal of the Ministry of Industry, Commerce and Handicraft

ABSTRACT OF THE INVENTION WITH MAIN DRAWING, DESCRIPTION AND CLAIMS

Application N. MI95 A000494 Reg.A Filing date 14/03/1995
Patent N. Granting date / /

D. TITLE

"Quinoline derivatives"

L.ABSTRACT

Novel quinoline derivatives, the processes for the preparation thereof and the use thereof in medicine for the treatment of pulmonary diseases, skin disorders and itch, neurogenic inflammation and CNS disorders.

M. DRAWING

4602 M
MaB/rt

Description of the industrial invention having title:
"QUINOLINE DERIVATIVES"
in the name of : **SmithKline Beecham Farmaceutici S.p.A.**
with head-offices in: Baranzate di Bollate (Milano)

* * *

The present invention relates to novel quinoline derivatives, processes for their preparation and their use in medicine.

The mammalian peptide Neurokinin B (NKB) belongs to the Tachykinin (TK) peptide family which also include Substance P (SP) and Neurokinin A (NKA). Pharmacological and molecular biological evidence has shown the existence of three subtypes of TK receptor (NK_1, NK_2 and NK_3) and NKB binds preferentially to the NK_3 receptor although it also recognises the other two receptors with lower affinity (Maggi et al , **1993**, *J. Auton. Pharmacol., 13*, 23-93).

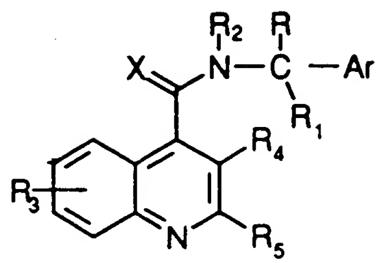
Selective peptidic NK_3 receptor antagonists are known (Drapeau, **1990** *Regul. Pept.*, 31, 125-135), and findings with peptidic NK_3 receptor agonists suggest that NKB, by activating the NK_3 receptor, has a key role in the modulation of neural input in airways, skin, spinal cord and nigro-striatal pathways (Myers and Undem, 1993, J.Phisiol., 470, 665-679; Counture et al., 1993, Regul. Peptides, 46, 426-429; Mccarson and Krause, 1994, J. Neurosci., 14 (2), 712-720; Arenas et al. 1991, J.Neurosci., 11, 2332-8).

However, the peptide-like nature of the known antagonists makes them likely to be too labile from a metabolic point of view to serve as practical therapeutic agents.

We have now discovered a novel class of selective, non-peptide NK_3 antagonists which are far more stable from a metabolic point of view than the known peptidic NK_3 receptor antagonists and are of potential therapeutic utility in treating pulmonary disorders (asthma, chronic obstructive pulmonary diseases -COPD-, airway hyperreactivity, cough), skin disorders and itch (for example, atopic dermatitis and cutaneous wheal and flare), neurogenic inflammation and CNS disorders (Parkinson's disease, movement disorders, anxiety). These disorders are referred to hereinafter as the Primary Disorders.

The novel NK_3 antagonists of the present invention are also of potential therapeutic utility in treating convulsive disorders, epilepsy, renal disorders, urinary incontinence, ocular inflammation, inflammatory pain, eating disorders (food intake inhibition), allergic rhinitis, neurodegenerative disorders (for example Alzheimer's disease), psoriasis, Huntington's disease, and depression (hereinafter referred to as the Secondary Disorders).

According to the present invention there is provided a compound, or a solvate or salt thereof, of formula (I):



(I)

in which:

Ar is an optionally substituted phenyl, naphthyl or C_{5-7} cycloalkdienyl group, or an optionally substituted single or fused ring heterocyclic group, having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from S, O, N;

R is linear or branched C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkylalkyl, optionally substituted phenyl or phenyl C_{1-6} alkyl, optionally substituted five-membered heteroaromatic rings comprising up to four heteroatom selected from among O or N, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, C_{1-6} alkylaminoalkyl, di C_{1-6} alkylaminoalkyl, C_{1-6} acylaminoalkyl, C_{1-6} alkoxyalkyl, C_{1-6} alkylcarbonyl, carboxy, C_{1-6} alkoxyxcarbonyl, C_{1-6} alkoxycarbonyl C_{1-6} alkyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di C_{1-6} alkylaminocarbonyl, halogeno C_{1-6} alkyl; or is a group $-(CH_2)_p-$ when cyclized onto Ar, where p is 2 or 3.

R_1 and R_2, which may be the same or different, are independently hydrogen or C_{1-6} linear or branched alkyl, or together form a -(CH2)n- group in which n represents 3, 4, or 5; or R_1 together with R forms a group $-(CH_2)_q-$, in which q is 2, 3, 4 or 5.

R_3 and R_4, which may be the same or different, are independently hydrogen, C_{1-6} linear or branched alkyl, C_{1-6} alkenyl, aryl, C_{1-6} alkoxy, hydroxy, halogen, nitro, cyano, carboxy, carboxamido, sulphonamido, C_{1-6} alkoxycarbonyl, trifluoromethyl, acyloxy, phthalimido, amino, $-O(CH_2)_r-NT_2$, in which r is 2, 3, or 4 and T is hydrogen or C_{1-6} alkyl; $-O(CH_2)_s-OW_2$ in which s is 2, 3, or 4 and W is hydrogen or C_{1-6} alkyl; hydroxyalkyl, aminoalkyl, mono-or di-alkylaminoalkyl, acylamino, alkylsulphonylamino, aminoacylamino, mono- or di-alkylaminoacylamino; with up to four R_3 substituents being present in the quinoline nucleus;

orR$_4$ is a group $-(CH_2)_t-$ when cyclized onto R_5 as aryl, in which t is 1, 2, or 3;

R_5 is branched or linear C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkylalkyl, optionally substituted aryl, or an optionally substituted single or fused ring heterocyclic group, having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from S, O, N;

X is O, S, or N-C≡N.

Preferably, Ar is phenyl optionally substituted by hydroxy, halogen, C_{1-6} alkoxy or trifluoromethyl. Examples of halogen are chlorine and fluorine, and an example of C_{1-6} alkoxy is methoxy.

Examples of Ar as a heterocyclic group are furyl, thienyl, pyridyl, pyrryl, thiazolyl, indolyl, benzofuryl or benzothienyl.

Examples of Ar as a C_{5-7} cycloalkdienyl group are cyclopentadienyl and cyclohexadienyl.

Examples of R are as follows:

C_{1-6} alkyl: methyl, ethyl, n-propyl, iso-propyl;

C_{3-7} cycloalkyl: cyclopropyl;

C_{4-7} cycloalkylalkyl: cyclopropylmethyl;

heteroaromatic rings: oxadiazoles, methyloxadiazoles;

hydroxy C_{1-6} alkyl: - CH_2OH, $-CH_2CH_2OH$, CH(Me)OH, $CH_2CH(Me)OH$;

amino C_{1-6} alkyl: $-CH_2NH_2$;

C_{1-6} alkylaminoalkyl: $-CH_2NHMe$, $-CH_2NHEt$;

di C_{1-6} alkylaminoalkyl: $-CH_2NHMe_2$, $-CH_2NHEt_2$;

C_{1-6} acylaminoalkyl: $-CH_2NHCOMe$;

C_{1-6} alkoxylalkyl: CH_2OMe;

C_{1-6} alkylcarbonyl: COMe;

C_{1-6} alkoxycarbonyl: COOMe; COOEt, -COOi-Pr;

C_{1-6} alkoxycarbonyl C_{1-6} alkyl: CH_2COOMe;

C_{1-6} alkylaminocarbonyl: CONHMe, -CONHEt;

di C_{1-6} alkylaminocarbonyl: $CONMe_2$, $-CONEt_2$, -CONMeEt:

halogen C_{1-6} alkyl: trifluoromethyl.

Examples of R_1 and R_2 are methyl, ethyl and n-propyl.

Examples of R_3 and R_4 are methyl, ethyl, n-propyl, methoxy, ethoxy, hydroxy, amino, chlorine, fluorine, bromine, methoxycarbonyl and phenyl.

Examples of R_5 are iso-propyl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclohexylmethyl, phenyl optionally substituted as defined for Ar above, and the heterocyclic groups as defined for Ar above.

A preferred group of compounds of formula (I) are those in which:

Ar is phenyl, 2-thienyl or cyclohexadienyl;

R is methyl, ethyl, n-propyl, -COOMe, -COMe;

R_1 and R_2 are each hydrogen or methyl;

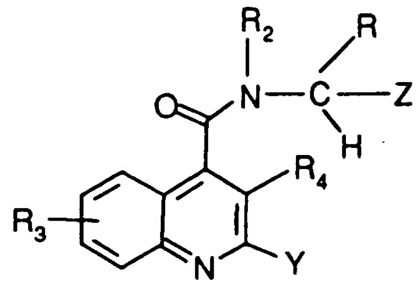
R_3 is hydrogen, methoxy, or hydroxy;

R_4 is hydrogen, methyl, ethyl, methoxy, hydroxy, amino, chlorine, bromine, dimethylaminoethoxy;

R_5 is phenyl, 2-thienyl, 2-furyl, 2-pyrryl and 3-thienyl;

and X is oxygen.

A preferred sub-group of compounds within the scope of formula (I) above is of formula (Ia):

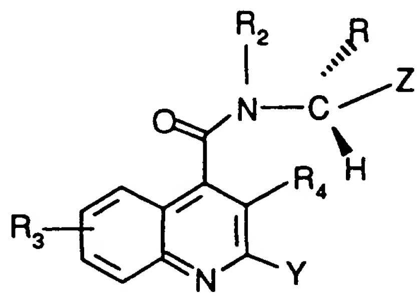


(Ia)

in which:

R, R_2, R_3 and R_4 are as defined in formula (I), and Y and Z, which may be the same or different, are each Ar as defined in formula (I).

A particularly preferred group of compounds of formula (Ia) are those of formula (Ib) in which the group R is oriented downward and H upward.



(Ib)

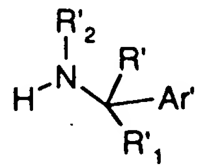
The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.
A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the compound of formula (I) or its salt or solvate.
One preferred pharmaceutically acceptable form is the crystalline form, including such form in pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Examples of pharmaceutically acceptable salts of a compound of formula (I) include the acid addition salts with the conventional pharmaceutical acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic, and methanesulphonic.

Examples of pharmaceutically acceptable solvates of a compound of formula (I) include hydrates.

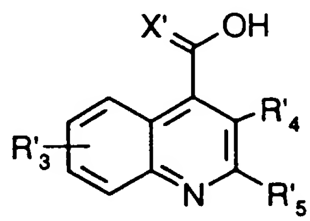
The compounds of formula (I) may have at least one asymmetric centre and therefore may exist in more than one stereoisomeric form. The invention extends to all such forms and to mixtures thereof, including racemates.

The invention also provides a process for the preparation of a compound of formula (I) which comprises reacting a compound of formula (III)



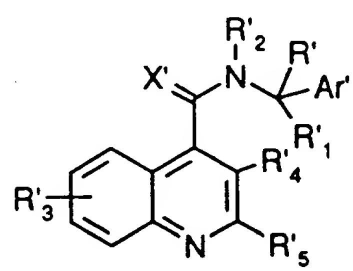
(III)

in which R', R'_1, R'_2 and Ar' are R, R_1, R_2 and Ar as defined for formula (I) or a group or atom convertible to R, R_1, R_2 and Ar, with a compound of formula (II)



(II)

or an active derivative thereof, in which R'_3, R'_4, R'_5 and X' are R_3, R_4, R_5 and X as defined for formula (I) or a group convertible to R_3, R_4, R_5 and X, to form a compound of formula (Ic)



(Ic)

and optionally thereafter performing one or more of the following steps:

(a) where R', R'_1 to R'_5, Ar' and X' are other than R, R_1 to R_5, Ar and X, converting any one of R', R'_1 to R'_5, Ar' and X' to R, R_1 to R_5, Ar and X to obtain a compound of formula (I),

(b) where R', R'_1 to R'_5, Ar' and X' are R, R_1 to R_5, Ar and X, converting any one of R, R_1 to R_5, Ar and X to another R, R_1 to R_5, Ar and X, to obtain a compound of formula (I),

(c) forming a salt and/or solvate of the obtained compound of formula (Ic).

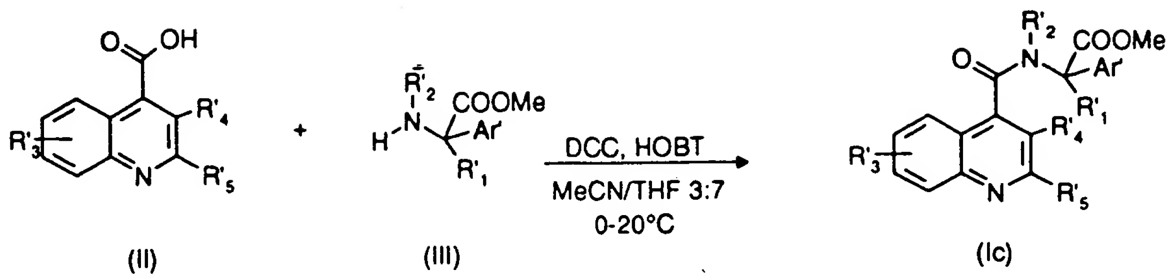
Suitable active derivatives of the compounds of formula (II) are acid halides (preferably chlorides), acid azides or acid anhydrides. Another suitable derivative is a mixed anhydride formed between the acid and an alkyl chloroformate; another suitable derivative is an activated ester such as a cyanomethyl ester, thiophenyl ester, p-nitrophenyl ester, p-nitrothiophenyl ester, 2,4,6-trichlorophenyl ester, pentachlorophenyl ester, pentafluorophenyl ester, N-hydroxy-phtalimido ester, N-hydroxypiperidine ester, N-hydroxysuccinimide ester, N-hydroxy benzotriazole ester; or the carboxy group may be activated using a carbodiimide or N,N'-carbonyldiimidazole.

For example, in standard methods well known to those skilled in the art, the compounds of formula (III) may be coupled:

(a) with an acid chloride in the presence of an inorganic or organic base in a suitable aprotic solvent such as dimethylformamide (DMF) at a temperature in a range from -70 to 50°C (preferably in a range from -10 to 20°C),

(b) with the acid in the presence of a suitable condensing agent, such as for example N,N'-carbonyl diimidazole (CDI) or a carbodiimide such as dicyclohexylcarbodiimide (DCC) or N-dimethylaminopropyl-N'-ethylcarbodiimide and N-hydroxybenzotriazole (HOBT) to maximise yields and avoid racemization processes (*Synthesis*, 453, **1972**) in an aprotic solvent such as a mixture of acetonitrile (MeCN) and tetrahydrofuran (THF) in a ratio from 1 : 9 to 7 : 3, respectively, at a temperature in a range from -70 to 50°C (preferably in a range from -10 to 25°C) (see Scheme 1),

Scheme 1



(c) with a mixed anhydride generated in situ from the acid and an alkyl (for example isopropyl) chloroformate in a suitable aprotic solvent such as dichloromethane at a temperature in a range from -70 to 50°C (preferably in a range from -20 to 20°C).

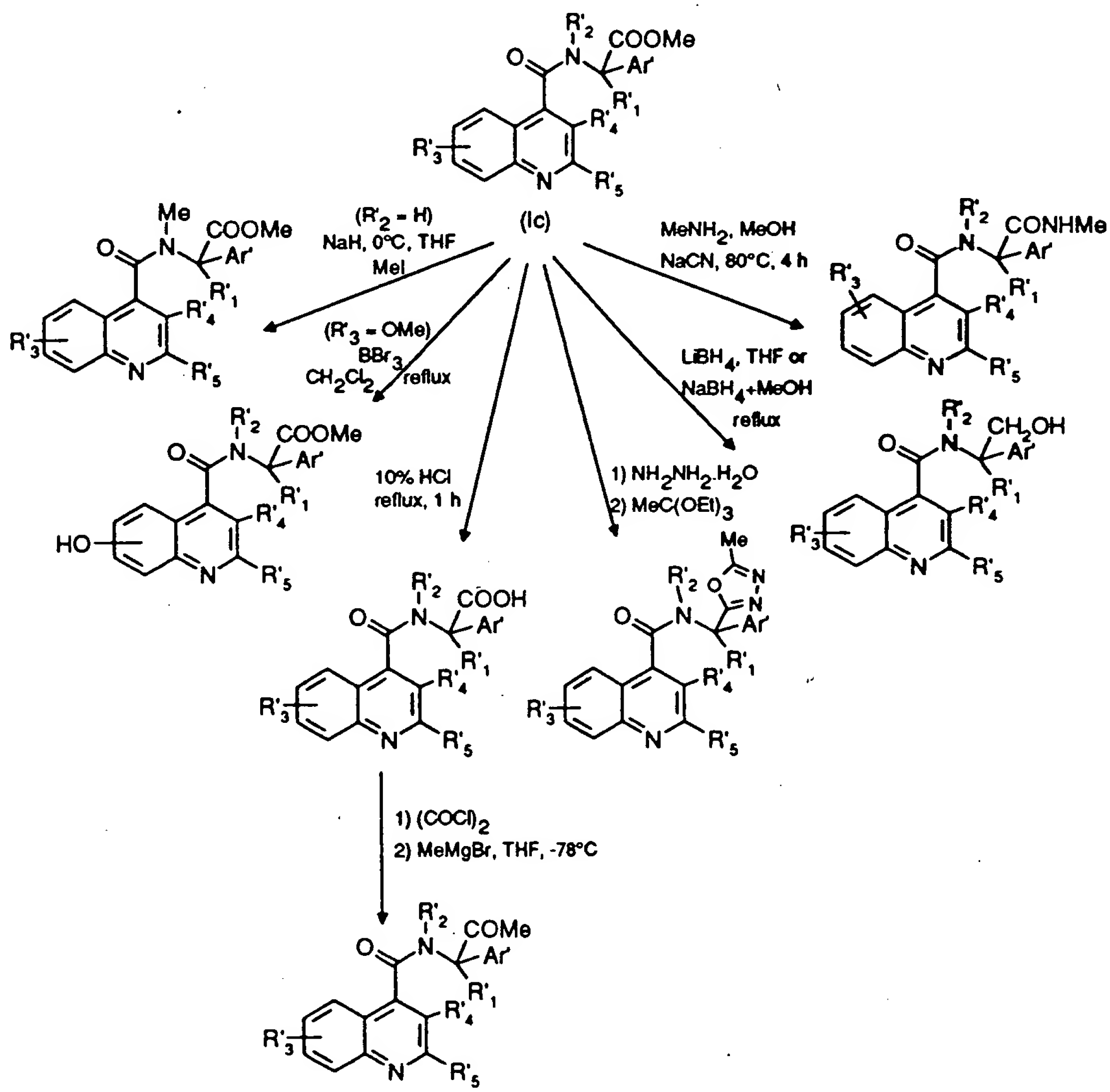
It will be appreciated that a compound of formula (Ic) may be converted to a compound of formula (I), or one compound of formula (I) may be converted to another compound of formula (I), by interconversion of suitable substituents. Thus, certain compounds of formula (I) and (Ic) are useful intermediates in forming other compounds of the present invention.

For example R'_2 may be hydrogen and converted to R_2 alkyl group, for example methyl, by conventional amide alkylation procedures (Zabicky, *The chemistry of amides*; Interscience, London, 1970, p. 749). When X' is oxygen, it may be converted to X sulphur by standard thioamide formation reagents, such as P_2S_5 (*Chem. Rev.*, *61*, 45, **1961** or *Angew. Chem.*, *78*, 517, **1966**) or the Lawesson reagent (*Tetrahedron*, *41*, 5061, **1985**). When Ar' or R'_5 is a methoxy substituted phenyl, it may be converted to another Ar' or R'_5 hydroxy substituted phenyl by standard demethylation procedures via Lewis acids, such as boron tribromide (*Synthesis*, 249, **1983**) or mineral acids, such as hydrobromic or hydroiodic acid. When R is an alkoxycarbonyl group, for example methoxycarbonyl, it may be converted to another R, such as ethoxycarbonyl by transesterification with an appropriate alcohol at a temperature in a range from 20 to 120°C, carboxy by hydrolysis in acidic or basic medium, aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl by transamidation with ammonia, a primary amine or a secondary amine in methanol as solvent at a temperature in a range from 10 to 120°C, optionally in the presence of a catalytic amount of NaCN (*J. Org. Chem.*, *52*, 2033, **1987**) or by using trimethylaluminium (Me_3Al) (*Tetrahedron Letters*, *48*, 4171, **1977**), hydroxymethyl by a selective metal hydride reduction, such as lithium borohydride reduction (*Tetrahedron*, *35*, 567, **1979**) or sodium borohydride reduction in THF + MeOH (*Bull. Chem. Soc. Japan*, *57*, 1948, **1984** or *Synth. Commun.*, *12*, 463, **1982**), alkylcarbonyl by acyl chloride formation and subsequent reaction with alkylmagnesium halides in THF as solvent at

a temperature in a range from -78 to 30°C (*Tetrahedron Letters*, 4303, **1979**) or with alkylcadmium halides or dialkylcadmium in the presence of $MgCl_2$ or LiCl (*J. Org. Chem.*, *47*, 2590, **1982**). Another group which R' as methoxycarbonyl can be converted into is a substituted heteroaromatic ring, such as an oxadiazole (*J. Med. Chem.*, *34*, 2726, **1991**).

Scheme 2 summarizes some of the above described procedures to convert a compound of formula (Ic) or (I) in which X' is oxygen, R' is COOMe, Ar' and R'_1 to R'_5 are as described for formula (I) to another compound of formula (I).

Scheme 2



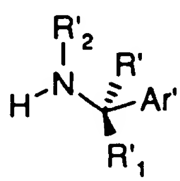
The compounds of formula (I) may be converted into their pharmaceutically acceptable acid addition salts by reaction with the appropriate organic or mineral acids.

Solvates of the compounds of formula (I) may be formed by crystallization or recrystallization from the appropriate solvent. For example, hydrates may be formed

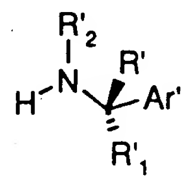
by crystallization or recrystallization from aqueous solutions, or solutions in organic solvents containing water.

Also salts or solvates of the compounds of formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the production of pharmaceutically acceptable salts or solvates. Accordingly such salts or solvates also form part of this invention.

As mentioned before, the compounds of formula (I) may exist in more than one stereoisomeric form and the process of the invention may produce racemates as well as enantiomerically pure forms. To obtain pure enantiomers, appropriate enantiomerically pure primary or secondary amines of formula (IIId) or (IIIe)

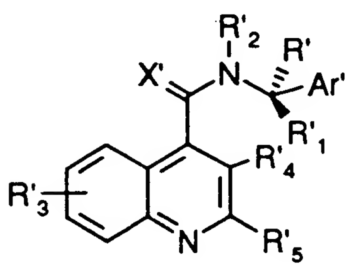


(IIId)

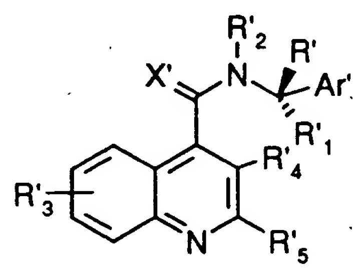


(IIIe)

are reacted with compounds of formula (II), to obtain compounds of formula (I'd) or (I'e).

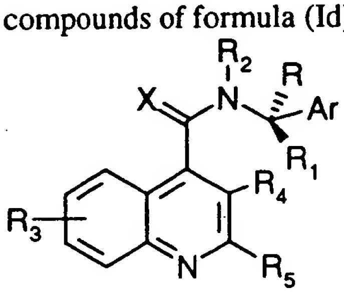


(I'd)

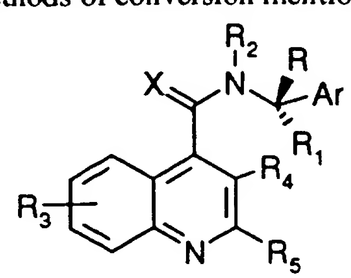


(I'e)

Compounds of formula (I'd) or (I'e) may subsequently be converted to compounds of formula (Id) or (Ie) by the methods of conversion mentioned before.



(Id)



(Ie)

Compounds of formula (II) are known compounds or can be prepared from known compounds by known methods.

For example, the compound of formula (II), in which X' is oxygen, R'_3, R'_4 and R'_5 are hydrogen is described in Pfitzinger, *J. Prakt. Chem.*, *38*, 582, **1882** and in Pfitzinger, *J. Prakt. Chem.*, *56*, 293, **1897**; the compound of formula (II), in which X' is oxygen, R'_3 and R'_4 are hydrogen and R'_5 is 2-pyridyl is described in Risaliti, *Ric. Scient.*, *28*, 561, **1958**; the compound of formula (II), in which X' is oxygen, R'_3 and R'_4 are hydrogen and R'_5 is *o*-, *m*- and *p*-chlorophenyl, *o*-fluorophenyl and 3,4-dichlorophenyl are described in Brown *et al.*, *J. Am. Chem. Soc.*, *68*, 2705, **1946**; the compound of formula (II), in which X' is oxygen, R'_3 and R'_4 are hydrogen and R'_5 is *p*-methoxyphenyl is described in Ciusa and Luzzatto, *Gazz. Chim. Ital.*, *44*, 64, **1914**; the compound of formula (II), in which X' is oxygen, R'_3 and R'_4 are hydrogen and R'_5 is *m*-trifluoromethylphenyl is described in Shargier and Lalezari, *J. Chem. Eng. Data*, *8*, 276, **1963**; the compound of formula (II), in which X' is oxygen, R'_3 and R'_4 are hydrogen and R'_5 is *p*-fluorophenyl is described in Bu Hoi *et al.*, *Rec Trav. Chim.*, *68*, 781, **1949**; the compound of formula (II), in which X' is oxygen, R'_3 and R'_4 are hydrogen and R'_5 is *p*-methylphenyl is described in Prevost *et al.*, *Compt. Rend. Acad. Sci.*, *258*, 954, **1964**; the compound of formula (II), in which X' is oxygen, R'_3 and R'_4 are hydrogen and R'_5 is *p*-bromophenyl is described in Nicolai *et al.*, *Eur. J. Med. Chem.*, 27, 977, **1992**; the compound of formula (II) in which X' is oxygen, R'_4 and R'_5 are hydrogen and R'_3 is 6-methyl is described in Buchmann and Howton, *J. Am. Chem. Soc.*, *68*, 2718, **1946**; the compound of formula (II), in which X' is oxygen, R'_4 and R'_5 are hydrogen and R'_3 is 8-nitro is described in Buchmann *et al*, *J. Am. Chem. Soc.*, *69*, 380, **1947**; the compound of formula (II), in which X' is oxygen, R'_4 is hydrogen, R'_3 is 6-chloro, R'_5 is p-chlorophenyl is described in Lutz *et al.*, *J. Am. Chem. Soc.*, *68*, 1813, **1946**; the compound of formula (II), in which X' is oxygen, R'_3 and R'_4 are hydrogen and R'_5 is 2-thiazolyl is described in **Eur. Pat. Appl. EP 112,776**; compounds of formula (II), in which X' is oxygen, R'_3 is 8-trifluoromethyl, R'_4 is hydrogen and R'_5 are phenyl, *o*- and *p*-fluorophenyl, 3,4-dichlorophenyl, *p*-methoxyphenyl are described in Nicolai *et al.*, *Eur. J. Med. Chem.*, 27, 977, **1992**; compounds of formula (II), in which X' is oxygen, R'_3 is 6-bromo, R'_4 is hydrogen and R'_5 are phenyl or *p*-fluorophenyl are described in Nicolai *et al.*, *Eur. J. Med. Chem.*, 27, 977, **1992**; other compounds of formula (II) are described in **Ger. Offen. DE 3,721,222** and in **Eur. Pat. Appl. EP 384,313**.

Compounds of formula (III), (IIId) and (IIIe) are commercially available compounds or can be prepared from known compounds by known methods (for example, compounds of formula (III) in which R' is alkoxycarbonyl, R'_1 and R'_2 are hydrogen and Ar' is as defined for the compounds of formula (I), are described in *Liebigs Ann. der Chemie*, *523*, 199, **1936**).

The activity of the compounds of formula (I) as NK_3 receptor antagonists in standard tests indicates that they are of potential therapeutic utility in the treatment of both the Primary and Secondary Disorders hereinbefore referred to.

The discovery that NK_3 receptor antagonists have potential therapeutic utility in treating the Secondary Disorders is new, and in a further aspect of the present invention there is provided the use of an NK_3 receptor antagonist for the treatment of the Secondary Disorders. There is also provided the use of an NK_3 receptor antagonist in the manufacture of a medicament for the treatment of any of the Secondary Disorders.

The present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

The present invention further provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of the Primary and Secondary Disorders.

Such a medicament, and a composition of this invention, may be prepared by admixture of a compound of the invention with an appropriate carrier. It may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the preparation of compositions of known agents for treating the conditions.

Preferably, a pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent in the treatment of the conditions.

The suitable dosage range for the compounds of the invention depends on the compound to be employed and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

The compound or composition of the invention may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinyl-pyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

The compounds of this invention may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example for rectal administration as a suppository. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or

solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi- dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

The compounds of this invention may also be administered by inhalation, via the nasal or oral routes. Such administration can be carried out with a spray formulation comprising a compound of the invention and a suitable carrier, optionally suspended in, for example, a hydrocarbon propellant.

Preferred spray formulations comprise micronised compound particles in combination with a surfactant, solvent or a dispersing agent to prevent the sedimentation of suspended particles. Preferably, the compound particle size is from about 2 to 10 microns.

A further mode of administration of the compounds of the invention comprises transdermal delivery utilising a skin-patch formulation. A preferred formulation comprises a compound of the invention dispersed in a pressure sensitive adhesive which adheres to the skin, thereby permitting the compound to diffuse from the adhesive through the skin for delivery to the patient. For a constant rate of percutaneous absorption, pressure sensitive adhesives known in the art such as natural rubber or silicone can be used.

As mentioned above, the effective dose of compound depends on the particular compound employed, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20 mg of active ingredient and be administered in multiples, if desired, to give the preceding daily dose.

No unacceptable toxicological effects are expected with compounds of the invention when administered in accordance with the invention.

The present invention also provides a method for the treatment and/or prophylaxis of the Primary and Secondary Conditions in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The invention further provides a method for the treatment and/or prophylaxis of the Secondary Conditions in mammals, particularly humans, which comprises

administering to the mammal in need of such treatment and/or prophylaxis an effective amount of an NK_3 receptor antagonist.

The activity of the compounds of the present invention, as NK_3 ligands, is determined by their ability to inhibit the binding of the radiolabelled NK_3 ligands, $[^{125}I]$-[Me-Phe^7]-NKB or $[^3H]$-Senktide, to guinea-pig and human NK_3 receptors (Renzetti et al, **1991**, *Neuropeptide, 18*, 104-114; Buell et al, **1992**, *FEBS, 299(1)*, 90-95; Chung et al, **1994**, *Biochem. Biophys. Res. Commun., 198(3)*, 967-972).
The binding assays utilized allow the determination of the concentration of the individual compound required to reduce by 50% the $[^{125}I]$-[Me-Phe^7]-NKB and $[^3H]$-Senktide specific binding to NK_3 receptor in equilibrium conditions.
Binding assays provide for each compounds tested means of IC_{50} values of 2-5 separate experiments performed in triplicate or in quadruplicate. The most potent compounds of the present invention show IC_{50} values in the range 1-1000 nM; in particular, in guinea-pig cortex membranes by displacement of $[^3H]$-Senktide, the compounds of the Examples 22, 47, 48, and 85 display K_is (nM) of 5.6, 8.8, 12.0 and 4.8 respectively (n=3). The NK_3-antagonist activity of the compounds of the present invention is determined by their ability to inhibit Senktide induced contraction of the guinea-pig ileum (Maggi et al, **1990**, *Br. J. Pharmacol., 101*, 996-1000) and human NK_3 receptors-mediated Ca^{++} mobilization (Mochizuki et al, **1994**, *J. Biol. Chem., 269*, 9651-9658). Guinea-pig functional assay provide for each compound tested means of K_B values of 3-8 separate experiments, where K_B is the concentration of the individual compound required to produce a 2-fold rightward shift in the dose-response curve of Senktide. Human receptor functional assay allows the determination of the concentration of the individual compound required to reduce by 50% (IC_{50} values) the Ca^{++} mobilization induced by the agonist NKB. In this assay, the compounds of the present invention behave as antagonists.
The therapeutic potential of the compounds of the present invention in treating the conditions can be assessed using rodent disease models.

The following Descriptions illustrate the preparation of the intermediates, whereas the Examples illustrate the preparation of the compounds of the present invention. The compounds of the Examples are summarised in the Tables 1 to 5

I.R. (KBr): 3420; 1630 cm^{-1}.

DESCRIPTION 3

2-phenyl-7-methoxy-4-quinolinecarbonyl chloride

2.8 ml (32.3 mmol) of oxalyl chloride are dissolved in 60 ml of CH_2Cl_2. The solution is cooled to -10°C and 6 g (19.0 mmol) of 7-methoxy-2-phenyl-4-quinolinecarboxylic acid are added, in more portions. The reaction mixture is left to stand overnight at room temperature and then evaporated to dryness _in vacuo_. 7.0 g of the desired product are obtained, which is used without further purifications.

$C_{17}H_{12}ClNO_2$

M.W. = 297.74

DESCRIPTION 4

2-phenyl-7-hydroxy-4-quinolinecarboxylic acid hydroiodide

1.5 g (5.4 mmol) of 7-methoxy-2-phenyl-4-quinolinecarboxylic acid are added, in more portions, to 50 ml of 57% HI. The reaction mixture is heated to reflux under strong magnetic stirring for 5 hours and then evaporated to dryness _in vacuo_ to yield 2.1 g of the desired product.

$C_{16}H_{11}NO_3 \cdot HI$

M.W. = 393.17

I.R. (KBr): 3120; 1650; 1620 cm^{-1}.

DESCRIPTION 5

2-(2-thienyl)-4-quinolinecarboxylic acid

5 g (34.0 mmol) of isatin, 4.4 ml (40.8 mmol) of 2-acetylthiophene and 6.3 g (112.2 mmol) of potassium hydroxide are dissolved in 40 ml of absolute EtOH and the suspension is heated at 80°C for 16 hours. The

DESCRIPTION 1

2-phenyl-4-quinolinecarbonyl chloride

11.7 ml (136.3 mmol) of oxalyl chloride are dissolved in 150 ml of CH_2Cl_2. The solution is cooled to -10°C and 20 g (80.2 mmol) of 2-phenyl-4-quinolinecarboxylic acid (commercially available are added, in more portions. The reaction mixture is left to stand, overnight at room temperature and then evaporated to dryness in vacuo. 22 g of the desired product are obtained, which is used without further purifications.

$C_{16}H_{10}ClNO$

M.W. = 267.76

DESCRIPTION 2

2-phenyl-7-methoxy-4-quinolinecarboxylic acid

5 g (28.2 mmol) of 6-methoxyisatin, 4 ml (33.8 mmol) of acetophenone and 5.2 g (92.6 mmol) of potassium hydroxide are dissolved in 22.9 ml of absolute EtOH and the suspension is heated at 80°C for 42 ore. The reaction mixture is cooled, 50 ml of water are added and the solution is extracted with 50 ml of Et_2O. The aqueous phase, cooled with ice, is acidified to pH 1 with 37% HCl and the precipitate is collected by filtration, washed with water and dried in vacuo a 40°C. 7.0 g of the desired product are obtained.

$C_{17}H_{13}NO_3$

M.P. = 226-228°C

M.W. = 279.30

Elemental analysis:

Calculated: C, 73.11; H, 4.69; N, 5.01;

Found: C, 72.07; H, 4.59; N, 4.90.

-10°C and 8.5 g (35.5 mmol) of 2-(2-furyl)-4-quinolinecarboxylic acid are added, in more portions. The reaction mixture is left to stand overnight at room temperature and then evaporated to dryness in vacuo. 9.2 g of the desired product are obtained, which is used without further purifications.

$C_{14}H_8ClNO_2$

M.W. = 257.78

DESCRIPTION 8

2-(4-pyridyl)-4-quinolinecarboxylic acid hydrochloride

5 g (34.0 mmol) of isatin, 4.5 ml (40.8 mmol) of 4-acetylpyridine and 6.3 g (112.2 mmol) of potassium hydroxide are dissolved in 40 ml of absolute EtOH and the suspension is heated at 80°C for 12 hours. The reaction mixture is cooled, 50 ml of water are added and the solution is extracted with 50 ml of Et_2O. The aqueous phase, cooled with ice, is acidified to pH 1 with 37% HCl and the precipitate is collected by filtration and washed with water. The aqueous solution is evaporated to dryness in vacuo, the residue is triturated with EtOH and filtered off. Evaporation of the solvent yields 6.0 g of crude which, combined with the precipitate previously obtained, is recrystallized from toluene containing MeOH traces. 4.5 g of the desired product are obtained.

$C_{15}H_{10}N_2O_2.HCl$

M.P. = 297-301°C

M.W. = 286.72

I.R. (KBr): 1705; 1635; 1610 cm-1.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 8.90 (d, 2H); 8.70 (m, 2H); 8.50 (s, 2H); 8.28 (d, 1H); 7.89 (dt, 2H).

reaction mixture is cooled, 50 ml of water are added and the solution is extracted with 50 ml of Et_2O. The aqueous phase, cooled with ice, is acidified to pH 1 with 37% HCl and the precipitate is collected by filtration, washed with water, dried in vacuo at 40°C and triturated with AcOEt. 4.8 g of the desired product are obtained.

$C_{14}H_9NO_2S$

M.P. = 181-183°C

M.W. = 255.29

I.R. (KBr): 1620 cm^{-1}.

300 MHz ^1H-NMR (DMSO-d_6): δ 8.60 (d, 1H); 8.45 (s, 1H); 8.10 (m, 2H); 7.78 (m, 2H); 7.68 (t, 1H); 7.22 (m, 1H).

DESCRIPTION 6

2-(2-furyl)-4-quinolinecarboxylic acid

5 g (34.0 mmol) of isatin, 4 ml (40.8 mmol) of 2-acetylfuran and 6.3 g (112.2 mmol) of potassium hydroxide are dissolved in 40.9 ml of absolute EtOH and the suspension is heated at 80°C for 12 hours. The reaction mixture is cooled, 50 ml of water are added and the solution is extracted with 50 ml of Et_2O. The aqueous phase, cooled with ice, is acidified to pH 1 with 37% HCl and the precipitate is collected by filtration, washed with water and dried in vacuo at 40°C. 8.5 g of the desired product are obtained.

$C_{14}H_9NO_3$

M.W. = 239.23

DESCRIPTION 7

2-(2-furyl)-4-quinolinecarbonyl chloride

5.2 ml (60.4 mmol) of oxalyl chloride are dissolved in 70 ml of CH_2Cl_2. The solution is cooled to

yield 1.1 g of the desired product.

$C_{24}H_{20}N_2O$

M.P. = 156-157°C

M.W. = 352.43

Elemental analysis:

Calculated: C, 81.79; H, 5.72; N, 7.95;

Found: C, 81.99; H, 5.69; N, 7.89.

I.R. (KBr): 3240;1645 cm^{-1}.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 9.29 (d, 1H); 8.32 (d, 2H); 8.13 (d, 1H); 8.13 (s, 1H); 8.06 (d, 1H); 7.81 (ddd, 1H); 7.68-7.52 (m, 4H); 7.47 (d, 2H); 7.39 (dd, 2H); 7.27 (dd, 1H); 5.30 (dq, 1H); 1.52 (d, 3H).

MS (EI; source 200 C; 70 V; 200 mA): 352 (M+.); 337; 232; 204; 77.

EXAMPLE 2

S-(+)-N-(α-methylbenzyl)-2-phenylquinoline-4-carboxamide

Prepared as described in Example 1 starting from 1.2 ml (9.4 mmol) of S-(-)-α-methylbenzylamine, 1.6 ml (11.7 mmol) of TEA, 2.0 g (7.8 mmol) of 2-phenyl-4-quinolinecarbonyl chloride in 100 ml of a CH_2Cl_2, CH_3CN and DMF mixture. The reaction mixture is worked up as described in Example 1. The residual oil is crystallized from AcOEt to yield 1.1 g of the desired product.

$C_{24}H_{20}N_2O$

M.P. = 161-162°C

M.W. = 352.43

$[\alpha]_D^{20}$ = + 25 (C = 0.5, DMF)

I.R. (KBr): 3240; 1645 cm^{-1}.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 9.29 (d, 1H); 8.32 (d, 2H);

DESCRIPTION 9

2-(4-pyridyl)-4-quinolinecarbonyl chloride hydrochloride

1.3 ml (10.4 mmol) of oxalyl chloride are dissolved in 60 ml of CH_2Cl_2. The solution is cooled to -10°C and 3.0 g (14.4 mmol) of 2-(4-pyridyl)-4-quinolinecarboxylic acid hydrochloride are added, in more portions. The reaction mixture is left to stand at room temperature, for 72 hours and then evaporated to dryness in vacuo. 4.0 g of the desired product are obtained, which is used without further purifications.

$C_{15}H_9ClN_2O \cdot HCl$

M.W. = 305.22

EXAMPLE 1

(R,S)-N-(α-methylbenzyl)-2-phenylquinoline-4-carboxamide

1.2 ml (9.4 mmol) of (R,S) α-methylbenzylamine and 1.6 ml (11.7 mmol) of triethylamine (TEA) are dissolved, under nitrogen, in 50 ml of an anhydrous CH_2Cl_2 and CH_3CN 1:1 mixture. 2.0 g (7.8 mmol) of 2-phenyl-4-quinolinecarbonyl chloride, dissolved in 50 ml of an anhydrous CH_2Cl_2 and DMF mixture 1:4, are dropped into the amine solution, cooled with an ice bath. The reaction is kept for 1 hour from 0° to 5°C and then at room temperature overnight. The reaction mixture is evaporated to dryness in vacuo and the residue is dissolved in AcOEt and washed twice with a saturated solution $NaHCO_3$. The organic phase is separated, dried over Na_2SO_4, filtered and evaporated to dryness in vacuo.

The residual oil is crystallized from AcOEt to

8.13 (d, 1H); 8.13 (s, 1H); 8.06 (d, 1H); 7.81 (ddd, 1H); 7.68-7.52 (m, 4H); 7.47 (d, 2H); 7.39 (dd, 2H); 7.27 (dd, 1H); 5.30 (dq, 1H); 1.52 (d, 3H).

The mass spectrum is the same as the one of Example 1.

EXAMPLE 3

R-(-)-N-(α-methylbenzyl)-2-phenylquinoline-4-carboxamide

Prepared as described in Example 1 starting from 1.2 ml (9.4 mmol) of R-(+)-α-methylbenzylamine 1.6 ml (11.7 mmol) of TEA, 2.0 g (7.8 mmol) of 2-phenyl-4-quinolinecarbonyl chloride in 100 ml of a CH_2Cl_2, CH_3CN and DMF mixture.

The reaction mixture is worked up as described in Example 1. The residual oil is crystallized from AcOEt to yield 1.1 g of the desired product.

$C_{24}H_{20}N_2O$

M.P. = 158-160°C

M.W. = 352.43

$[\alpha]_D^{20}$ = -25 (C = 0.5, DMF)

I.R. (KBr): 3240; 1645 cm^{-1}.

^{1}H-NMR and mass spectra are the same as those of Examples 1 and 2.

EXAMPLE 4

(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-phenylquinoline-4-carboxamide

2.0 g (8.0 mmol) of 2-phenyl-4-quinolinecarboxylic acid are dissolved, under nitrogen, in 130 ml of anhydrous THF and 100 ml of CH_3CN. 2.0 g (9.9 mmol) of (D,L) phenylglycine methyl ester hydrochloride and 1.5 ml (10.7 mmol) of TEA are added and the reaction

mixture is cooled to 5°C.

2.5 g (12.1 mmol) of dicyclohexylcarbodiimide (DCC), dissolved in 10 ml of anhydrous CH_2Cl_2, are dropped therein and the reaction is left to warm at room temperature overnight.

The precipitated dicyclohexylurea is filtered off and the solution is evaporated to dryness <u>in vacuo</u>. The residue is dissolved in CH_2Cl_2 and washed with water. The separated organic phase is dried over Na_2SO_4 and evaporated to dryness <u>in vacuo</u> to obtain 6.0 g of crude product which is dissolved in 20 ml of CH_2Cl_2 and left to stand overnight. More dicyclohexylurea precipitates, which is filtered off.

The solution is evaporated to dryness <u>in vacuo</u> and the residue is flash chromatographed over silica gel (230-400 mesh) using as the eluent a hexane/AcOEt 3:2 mixture containing 0.5% of NH_4OH (28%). The resulting product is warm triturated with i-Pr_2O, filtered, washed and dried to yield 1.1 g of the desired product.

$C_{25}H_{20}N_2O_3$

M.P. = 170-172°C

M.W. = 396.45

Elemental analysis:

Calculated: C, 75.74; H, 5.09; N, 7.07;

Found: C, 75.88; H, 5.12; N, 7.06.

I.R. (nujol): 3240; 1750; 1670 cm^{-1}.

300 MHz ^1H-NMR (DMSO-d_6): δ 9.72 (d, 1H); 8.28 (dd, 2H); 8.20 (dd, 1H); 8.13 (dd, 1H); 8.11 (s, 1H); 7.83 (ddd, 1H); 7.66 (ddd, 1H); 7.60-7.50 (m, 5H); 7.47-7.37 (m, 3H); 5.78 (d, 1H); 3.72 (s, 3H).

MS (EI; source 200°C; 70 V; 200 mA): 396 (M+.); 337;

232; 204.

EXAMPLE 5

(+)-(S)-N-[α-(methoxycarbonyl)benzyl]-2-phenylquinoline-4-carboxamide

2.0 g (8.0 mmol) of 2-phenyl-4-quinolinecarboxylic acid are dissolved, under nitrogen, in 70 ml of anhydrous THF and 30 ml of CH_3CN.

1.7 g (8.4 mmol) of (L) phenylglycine methyl ester hydrochloride, 1.1 ml (9.9 mmol) of N-methylmorpholine and 2.1 g (15.5 mmol) of N-hydroxybenzotriazole (HOBT) are added thereto and the reaction mixture is cooled to 0°C. 1.85 g (9.0 mmol) of DCC, dissolved in 10 ml of anhydrous CH_2Cl_2, are dropped therein and the reaction is then kept at 0° to 5°C for 1 hour and at room temperature for 2 hours. The precipitated dicyclohexylurea is filtered off and the solution is evaporated to dryness in vacuo. The residue is dissolved in CH_2Cl_2 and washed with water, a $NaHCO_3$ sat. sol., 5% citric acid, a $NaHCO_3$ sat. sol. and NaCl sat. sol..

The separated organic phase is dried over Na_2SO_4 and evaporated to dryness in vacuo; the residue is dissolved in 20 ml of CH_2Cl_2 and left to stand overnight. More dicyclohexylurea precipitates, which is filtered off.

The solution is evaporated to dryness in vacuo to obtain 2.6 g of crude product which is triturated with petroleum ether, filtered, washed with $i\text{-}Pr_2O$ and recrystallized with 70 ml of i-PrOH to obtain 1.7 g of the desired product.

$C_{25}H_{20}N_2O_3$

M.P. = 180-181°C

M.W. = 396.45

I.R. (nujol): 3300; 1750; 1640 cm^{-1}.

$_D^{20}$ = +42.0 (C = 0.5, MeOH).

^{1}H-NMR and mass spectra are the same as those of Example 4.

EXAMPLE 6

(-)-(R)-N-[α-(methoxycarbonyl)benzyl]-2-phenylquinoline-4-carboxamide

Prepared as described in Example 5 from 2.0 g (8.0 mmol) of 2-phenyl-4-quinolinecarboxylic acid, 1.7 g (8.4 mmol) of (D) phenylglycine methyl ester hydrochloride, 1.1 ml (9.9 mmol) of N-methylmorpholine, 2.1 g (15.5 mmol) of HOBT and 1.85 g (9.0 mmol) of DCC in 70 ml of anhydrous THF and 30 ml of CH_3CN.

The reaction mixture is worked up as described in Example 5. The obtained crude product (3.5 g) is warm triturated twice with i-Pr_2O, filtered, washed and recrystallized with 80 ml of i-PrOH to obtain 2.3 g of the desired product.

$C_{25}H_{20}N_2O_3$

M.P. = 180-181°C

M.W. = 396.45

I.R. (nujol): 3300; 1750; 1640 cm^{-1}.

$[\alpha]_D^{20}$ = -42.0 (C = 0.5, MeOH).

^{1}H-NMR and mass spectra are the same as those of Examples 4 and 5.

EXAMPLE 7

(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-phenyl-7-methoxyquinoline-4-carboxamide

1.0 g (5.0 mmol) of (D,L) phenylglycine methyl

ester hydrochloride are dissolved, under nitrogen, in 30 ml of anhydrous DMF. 2.5 g (18.1 mmol) of anhydrous potassium carbonate are added and the solution is cooled to 0°C. 0.7 g (2.3 mmol) of the product of Description 3 are dropped therein, dissolved in 25 ml of anhydrous DMF, and the reaction is kept at 0° to 5°C for 1 hour and at room temperature overnight.

The reaction mixture is evaporated to dryness *in vacuo* and the residue is dissolved in AcOEt and washed twice with water. The separated organic phase is dried over Na_2SO_4, filtered and evaporated to dryness *in vacuo*.

The residual oil is flash chromatographed over silica gel (230-400 mesh) using as the eluent a hexane/AcOEt 3:2 mixture containing 0.5% NH_4OH (28%), to obtain 0.1 g of crude product which is triturated with i-Pr_2O. 0.08 g of the desired product are obtained.

$C_{26}H_{22}N_2O_4$

M.P. = 187-190°C

M.W. = 426.48

I.R. (KBr): 3220; 1750; 1660; 1620 cm^{-1}.

300 MHz ^{1}H-NMR ($CDCl_3$): δ 8.13-8.08 (m, 3H); 7.80 (s, 1H); 7.55-7.38 (m, 9H); 7.21 (dd, 1H); 7.02 (d broad, 1H); 5.88 (d, 1H); 3.97 (s, 3H); 3.80 (s, 3H).

MS (EI; source 200°C; 70 V; 200 mA): 426 (M+.); 367; 262; 234; 191; 77.

EXAMPLE 8

(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-phenyl-7-hydroxy-quinoline-4-carboxamide

Prepared as described in Example 5 from 2.1 g (5.3

mmol) of the product of Description 4, 1.08 g (5.3 mmol) of (D,L) phenylglycine methyl ester hydrochloride, 1.5 ml (10.7 mmol) of TEA, 1.7 g (12.5 mmol) of HOBT and 1.2 g (5.8 mmol) of DCC in 70 ml of anhydrous THF and 30 ml of CH_3CN.

The reaction mixture is worked up as described in Example 5. The obtained crude product is triturated with $i\text{-}Pr_2O$ and recrystallized twice from i-PrOH to obtain 0.06 g of the desired product.

$C_{25}H_{20}N_2O_4$

M.P. = 256-257°C

M.W. = 412.45

I.R. (KBr): 3270; 1750; 1650; 1620 cm^{-1}.

300 MHz ^1H-NMR (DMSO-d_6): δ 10.30 (s broad, 1H); 9.64 (d, 1H); 8.22 (d, 2H); 8.04 (d, 1H); 7.85 (s, 1H); 7.60-7.34 (m, 9H); 7.21 (dd, 1H); 5.74 (d, 1H); 3.71 (s, 3H).

MS (EI; source 200°C; 70 V; 200 mA): 412 (M+.); 353; 248; 220; 77.

EXAMPLE 9

(R,S)-N-[α-(carboxy)benzyl]-2-phenyl-7-methoxyquinoline-4-carboxamide hydrochloride

0.18 g (0.4 mmol) of the product of Example 7 are dissolved in 10 ml of 10% HCl and 5 ml of dioxane. The reaction mixture is heated to reflux with magnetic stirring for 3 hours and then evaporated to dryness *in vacuo*.

The crude product is warm triturated with AcOEt (containing some drops of EtOH) to yield 0.16 g of the desired product.

$C_{25}H_{20}N_2O_4 \cdot HCl$

M.P. = 228-230°C

M.W. = 448.91

I.R. (KBr): 3180; 1735; 1655; 1630 cm^{-1}.

300 MHz ^1H-NMR (DMSO-d_6): δ 9.6 (d, 1H); 8.26 (dd, 2H); 8.14 (d, 1H); 7.98 (s, 1H); 7.63-7.52 (m, 6H); 7.46-7.36 (m, 3H); 7.33 (dd, 1H); 5.66 (d, 1H); 3.98 (s, 3H).

MS (EI; source 200°C; 70 V; 200 mA): 412 (M+.); 368; 262; 234; 191; 77.

EXAMPLE 10

(R,S)-N-[α-(methylaminocarbonyl)benzyl]2-phenylquinoline-4-carboxamide

0.45 g (1.1 mmol) of the product of Example 4 are dissolved in 40 ml of $MeNH_2$/33% EtOH; after adding a catalytic amount of NaCN the reaction mixture is heated at 70°C for 1 hour in a Parr apparatus. The inner pressure rises to 40 psi.

The solution is thereafter evaporated to dryness <u>in vacuo</u> and the residue is triturated with water, filtered, dried and recrystallized with a i-PrOH (50 ml) and EtOH (30 ml) mixture to obtain 0.2 g of the desired product.

$C_{25}H_{21}N_3O_2$

M.P. = 261-263°C

M.W. = 395.47

Elemental analysis:

Calculated: C, 75.93; H, 5.35; N, 10.63;

Found: C, 75.65; H, 5.34; N, 10.55.

I.R. (KBr): 3300; 3270; 1660; 1635 cm^{-1}.

300 MHz ^1H-NMR (DMSO-d_6): δ 9.48 (d, 1H); 8.33-8.25 (m, 3H); 8.18-8.10 (m, 3H); 7.80 (ddd, 1H); 7.68-7.50 (m,

6H); 7.40-7.28 (m, 3H); 5.75 (d, 1H); 2.63 (d, 3H).

MS (EI; source 200°C; 70 V; 200 mA): 395 (M+.); 337; 232; 204; 77.

EXAMPLE 11

(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(2-thienyl)quinoline-4-carboxamide

Prepared as described in Example 5 from 2.0 g (7.3 mmol) of 2-(2-thienyl)-4-quinolinecarboxylic acid, 1.7 g (8.4 mmol) of (D,L) phenylglycine methyl ester hydrochloride, 1.1 ml (10 mmol) of N-methylmorpholine, 2.1 g (15.5 mmol) of HOBT and 1.85 g (9.0 mmol) of DCC in 70 ml of anhydrous THF and 30 ml of CH_3CN.

The reaction mixture is worked up as described in Example 5. The obtained crude product is crystallized from AcOEt and then recrystallized from absolute EtOH to obtain 0.9 g of the desired product.

$C_{23}H_{18}N_2O_3S$

M.P. = 178-180°C

M.W. = 402.47

Elemental analysis:

Calculated: C, 68.64; H, 4.51; N, 6.96;

Found: C, 67.50; H, 4.99; N, 7.43.

I.R. (KBr): 3300; 1745; 1645 cm^{-1}.

300 MHz ^1H-NMR (DMSO-d_6): δ 9.70 (d, 1H); 8.12 (d, 1H); 8.08 (s, 1H); 8.04 (d, 1H); 8.02 (d, 1H); 7.19 (t, 1H); 7.76 (d, 1H); 7.62 (t, 1H); 7.53 (d, 2H); 7.46-7.37 (m, 3H); 7.30 (dd, 1H); 5.68 (d, 1H); 3.68 (s, 3H).

MS (EI; source 200°C; 70 V; 200 mA): 402 (M+.); 343; 238; 210; 77.

EXAMPLE 12

(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(2-furyl)quinoli-

ne-4-carboxamide

Prepared as described in Example 1 from 7.2 g (35.5 mmol) of (D,L) phenylglycine methyl ester hydrochloride, 12.4 ml (88.8 mmol) of TEA and 9.1 g (35.5 mmol) of 2-(2-furyl)-4-quinolinecarbonyl chloride in 350 ml of a CH_2Cl_2, CH_3CN and DMF mixture. The reaction mixture is worked up as described in Example 1. The crude product is triturated with MeOH to yield 3.3 g of the desired product.

$C_{23}H_{18}N_2O_4$

M.P. = 178-180°C

M.W. = 386.40

Elemental analysis:

Calculated: C, 71.49; H, 4.70; N, 7.25;

Found: C, 71.67; H, 4.74; N, 7.17.

I.R. (KBr): 3300; 1750; 1650 cm^{-1}.

300 MHz ^1H-NMR (DMSO-d_6): δ 9.72 (d, 1H); 8.12 (d, 1H); 8.06 (d, 1H); 7.96 (dd, 1H); 7.92 (s, 1H); 7.80 (ddd, 1H); 7.62 (ddd, 1H); 7.52 (dd, 2H); 7.45-7.35 (m, 4H); 6.73 (dd, 1H); 5.77 (d, 1H); 3.74 (s, 3H).

MS (EI; source 200°C; 70 V; 200 mA): 386 (M+.); 327; 222; 194; 77.

EXAMPLE 13

(R,S)-N-[α-(methoxycarbonyl)benzyl]-2-(4-pyridyl)quinoline-4-carboxamide

Prepared as described in Example 1 from 3.4 g (16.7 mmol) of (D,L) phenylglycine methyl ester hydrochloride, 3.9 ml (27.8 mmol) of TEA and 3.0 g (11.1 mmol) of 2-(4-pyridyl)-4-quinolinecarbonyl chloride in 100 ml of a CH_2Cl_2, CH_3CN and DMF mixture. The reaction mixture is worked up as described in

Example 1. The crude product is recrystallized three times from AcOEt to yield 1.9 g of the desired product.

$C_{24}H_{19}N_3O_3$

M.P. = 172-174°C

M.W. = 397.43

Elemental analysis:

Calculated: C, 72.53; H, 4.82; N, 10.57;

Found: C, 71.87; H, 4.87; N, 10.44.

I.R. (KBr): 3240; 1750; 1670 cm^{-1}.

300 MHz ^1H-NMR ($DMSO-d_6$): δ 9.74 (d, 1H); 8.79 (dd, 2H); 8.27-8.17 (m, 5H); 7.89 (ddd, 1H); 7.74 (ddd, 1H); 7.54 (dd, 2H); 7.47-7.38 (m, 3H); 5.80 (d, 1H); 3.75 (s, 3H).

MS (EI; source 200°C; 70 V; 200 mA): 397 (M+.); 338; 233; 205; 77.

EXAMPLE 14

(R,S)-N-[α-(methoxycarbonyl)-2-thienylmethyl]-2-phenyl-quinoline-4-carboxamide

Prepared as described in Example 1 from 1.94 g (9.4 mmol) of (D,L) thienylglycine methyl ester hydrochloride, 2.7 ml (19.5 mmol) of TEA and 2.0 g (7.8 mmol) of 2-phenyl-4-quinolinecarbonyl chloride in 100 ml of a CH_2Cl_2, CH_3CN and DMF mixture. The reaction mixture is worked up as described in Example 1. The crude product is recrystallized three times from AcOEt to yield 0.66 g of the desired product.

$C_{23}H_{18}N_2O_3S$

M.P. = 144-145°C

M.W. = 402.47

Elemental analysis:

Calculated: C, 68.64; H, 4.51; N, 6.96;

Found: C, 68.81; H, 4.46; N, 6.96.

I.R. (KBr): 3295; 1745; 1640 cm^{-1}.

300 MHz ^1H-NMR ($CDCl_3$): δ 8.25 (dd, 1H); 8.22 (dd, 1H); 8.17 (dd, 2H); 7.95 (s, 1H); 7.78 (ddd, 1H); 7.60 (ddd, 1H); 7.56-7.45 (m, 3H); 7.35 (dd, 1H); 7.20 (d, 1H); 7.05 (dd, 1H); 7.05 (s broad, 1H); 6.22 (d, 1H); 3.90 (s, 3H).

MS (EI; source 200°C; 70 V; 200 mA): 402 (M+.); 343; 232; 204.

EXAMPLE 15

(R,S)-N-[α-(methoxycarbonylmethyl)benzyl]-2-phenylquinoline-4-carboxamide

Prepared as described in Example 5 from 1.39 g (5.6 mmol) of 2-phenyl-4-quinolinecarboxylic acid, 1.2 g (5.6 mmol) of methyl (R,S) 3-amino-3-phenylpropionate hydrochloride, 0.78 ml (5.6 mmol) of TEA, 1.51 g (11.2 mmol) of HOBT and 2.31 g (11.2 mmol) of DCC in 10 ml of anhydrous THF, 4 ml of CH_3CN and 7 ml of CH_2Cl_2. The reaction mixture is worked up as described in Example 5.

The crude product is dissolved in CH_2Cl_2 and left at 0°C overnight. The precipitated dicyclohexylurea is filtered off. The solution is evaporated to dryness in vacuo to obtain 1.4 g of crude product which is triturated with a i-Pr_2O/acetone 99:1 mixture. 1.2 g of the desired product are obtained.

$C_{26}H_{22}N_2O_3$

M.P. = 156-158°C

M.W. = 410.47

Elemental analysis:

Calculated: C, 76.07; H, 5.40; N, 6.82;

Found: C, 75.77; H, 5.38; N, 6.94.

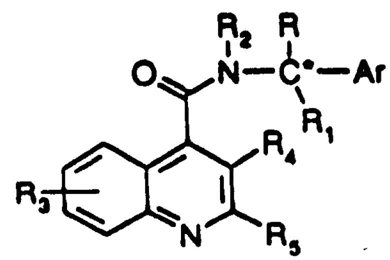
I.R. (KBr): 3295; 1755; 1645 cm^{-1}.

300 MHz ^{1}H-NMR (DMSO-d_6): δ 9.40 (d, 1H); 8.29 (dd, 2H); 8.14 (d, 1H); 8.07 (d, 1H); 8.04 (s, 1H); 7.83 (ddd, 1H); 7.66-7.52 (m, 4H); 7.50 (d, 2H); 7.40 (dd, 2H); 7.31 (ddd, 1H); 5.60 (dt, 1H); 3.65 (s, 3H); 3.04-2.89 (m, 2H).

MS (EI; source 200°C; 70 V; 200 mA): 410 (M+.); 337; 233; 205.

The characteristics of the compounds of the Examples are reported in the following Table.

TABLE 1



Ex.	Ar	R	R_1	R_2	R_3	R_4	R_5	*	Molecular Formula	M.P.°C	$[\alpha]_D^{20}$ c=0.5,MeOH
1	Ph	Me	H	H	H	H	Ph	(R,S)	$C_{24}H_{20}N_2O$	156-157	
2	Ph	Me	H	H	H	H	Ph	(S)	$C_{24}H_{20}N_2O$	161-162	+25° a
3	Ph	Me	H	H	H	H	Ph	(R)	$C_{24}H_{20}N_2O$	158-160	-25° a
4	Ph	COOMe	H	H	H	H	Ph	(R,S)	$C_{25}H_{20}N_2O_3$	170-172	
5	Ph	COOMe	H	H	H	H	Ph	(S)	$C_{25}H_{20}N_2O_3$	180-181	+42°
6	Ph	COOMe	H	H	H	H	Ph	(R)	$C_{25}H_{20}N_2O_3$	180-181	-42°
7	Ph	COOMe	H	H	7-OMe	H	Ph	(R,S)	$C_{26}H_{22}N_2O_4$	187-190	
8	Ph	COOMe	H	H	7-OH	H	Ph	(R,S)	$C_{25}H_{20}N_2O_4$	256-257	
9	Ph	COOH	H	H	7-OMe	H	Ph	(R,S)	$C_{25}H_{20}N_2O_4 \cdot HCl$	228-230	
10	Ph	CONHMe	H	H	H	H	Ph	(R,S)	$C_{25}H_{21}N_3O_2$	261-263	
11	Ph	COOMe	H	H	H	H	2-thienyl	(R,S)	$C_{23}H_{18}N_2O_3S$	178-180	
12	Ph	COOMe	H	H	H	H	2-furyl	(R,S)	$C_{23}H_{18}N_2O_4$	178-180	
13	Ph	COOMe	H	H	H	H	4-pyridyl	(R,S)	$C_{24}H_{19}N_3O_3$	172-174	
14		COOMe	H	H	H	H	Ph	(R,S)	$C_{23}H_{18}N_2O_3S$	144-145	
15	Ph	CH_2COOMe	H	H	H	H	Ph	(R,S)	$C_{26}H_{22}N_2O_3$	156-158	

[a] solvent DMF

The compounds of Examples 6-49 of general formula (I) (grouped together in the following Table 2) were prepared from the suitable acid chlorides of formula (II) and from the amines of formula (III) represented in the table, following the synthesis procedure described in Example 1. The acid chlorides were prepared from the corresponding acids of formula (II), following Description 1. The reaction yields were calculated on the purified, but not recrystallized, product. The analytical and spectroscopical data of Examples 16-49 are shown in Table 5.

TABLE 2

Acyl chloride of (II) + (III) -------- (I)

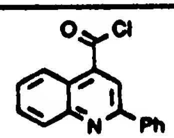
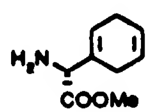
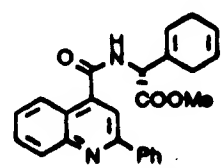
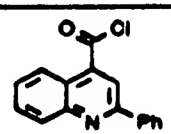
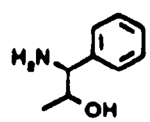
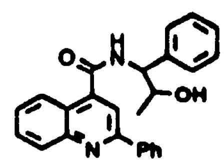
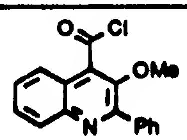
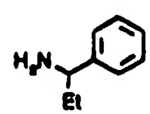
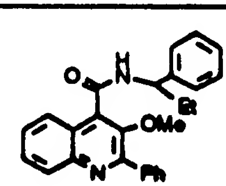
Ex.	Acyl chloride of (II)	(III)	(I)	Stereo chemi-stry	Molecular Formula	Molecular weight	Yield (%)	M.P. (°C) (cryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
16				(R)	$C_{25}H_{22}N_2O_3$	398.47	16	120-122 (iPr_2O)	- 18.9 (c=0.5)
17				(R,S) single diast.	$C_{25}H_{22}N_2O_2$	382.47	44	204-205 (iPrOH/ iPr_2O)	
18				(R,S)	$C_{26}H_{24}N_2O_2$	396.49	48	163-165 (iPrOH/ iPr_2O)	

TABLE 2 (continues)

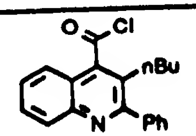
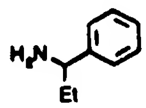
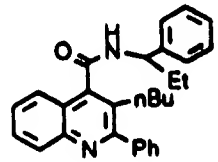
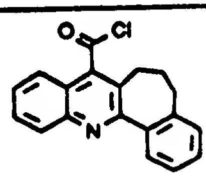
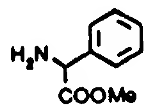
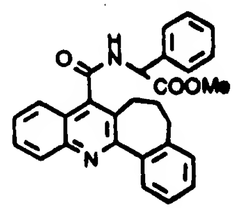
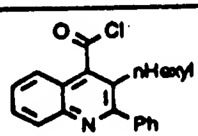
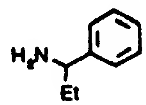
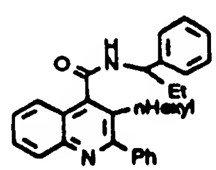
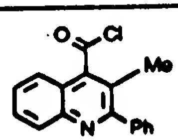
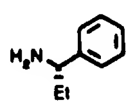
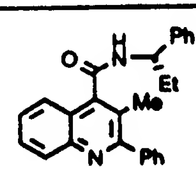
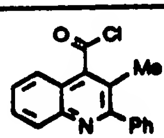
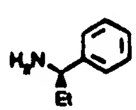
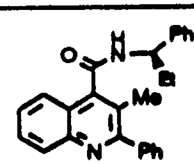
Ex.	Acyl chloride of (II)	(III)	(I)	Stereo chemi-stry	Molecular Formula	Molecular weight	Yield (%)	M.P. (°C) (cryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
19				(R,S)	$C_{29}H_{30}N_2O$	422.58	30	147-150 (esano)	
20				(R,S)	$C_{28}H_{24}N_2O_3$	436.52	43	186-188 (iPrOH/ iPr$_2$O)	
21				(R,S)	$C_{31}H_{34}N_2O$	450.63	24	131-134 (esano/ iPr$_2$O)	
22				(S)	$C_{26}H_{24}N_2O$	380.49	58	153-155 (iPr$_2$O)	- 36.0
23				(R)	$C_{26}H_{24}N_2O$	380.49	78	155-156 (iPr$_2$O)	+ 35.9

TABLE 2 (continues)

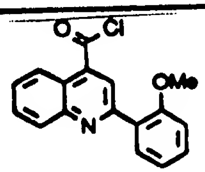
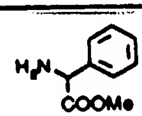
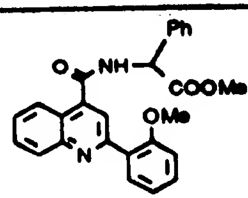
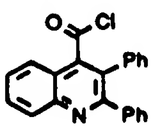
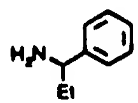
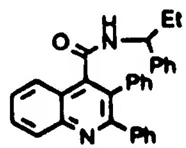
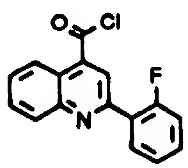
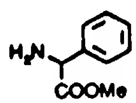
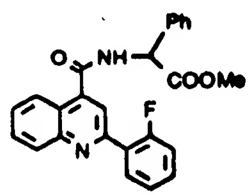
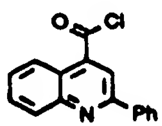
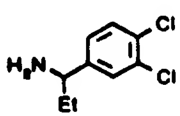
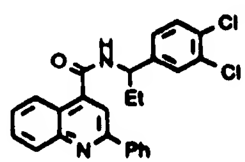
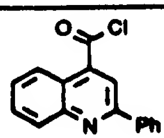
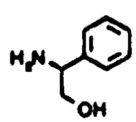
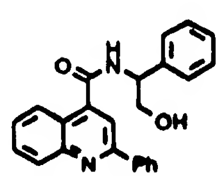
Ex.	Acyl chloride of (II)	(III)	(I)	Stereo chemi-stry	Molecular Formula	Molecular weight	Yield (%)	M.P. (°C) (cryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
24				(R,S)	$C_{26}H_{22}N_2O_4$	426.48	55	124-125 (toluene)	
25				(R,S)	$C_{31}H_{26}N_2O$	442.57	49	198-200 (toluene)	
26				(R,S)	$C_{25}H_{19}FN_2O_3$	414.44	75	146-147 (toluene)	
27				(R,S)	$C_{25}H_{20}Cl_2N_2O$	435.36	44	193-194 (toluene)	
28				(R,S)	$C_{24}H_{20}N_2O_2$	368.43	24	117-119 (toluene)	

TABLE 2 (continues)

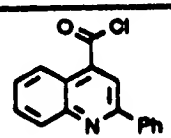
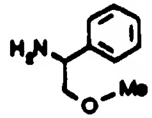
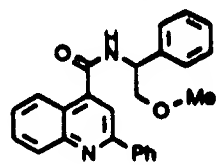
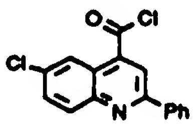
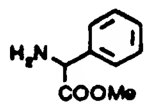
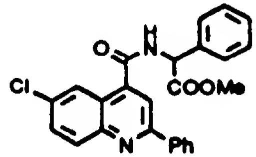
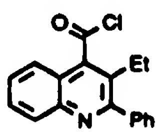
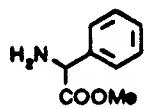
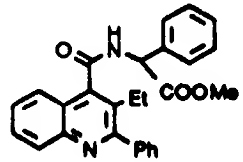
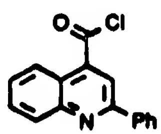
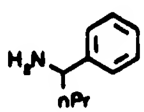
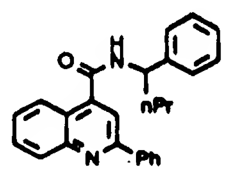
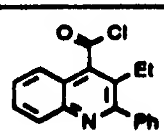
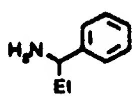
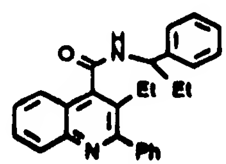
Ex.	Acyl chloride of (II)	(III)	(I)	Stereo chemi-stry	Molecular Formula	Molecular weight	Yield (%)	M.P. (°C) (cryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
34				(R,S)	$C_{25}H_{22}N_2O_2$	382.47	42	144-145 (toluene)	
35				(R,S)	$C_{25}H_{19}ClN_2O_3$	430.90	46	197-199 (toluene)	
36				(R,S)	$C_{27}H_{24}N_2O_3$	424.50	52	156-157 (toluene/ esano)	
37				(R,S)	$C_{26}H_{24}N_2O$	380.49	50	149-150 (toluene)	
38				(R,S)	$C_{27}H_{26}N_2O$	394.52	53	158-159 (Et_2O/ iPr_2O)	

TABLE 2 (continues)

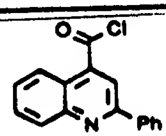
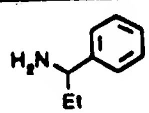
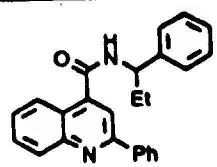
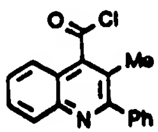
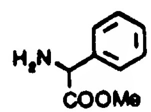
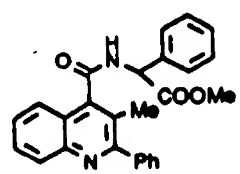
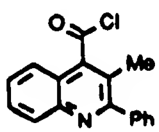
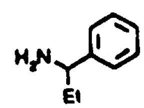
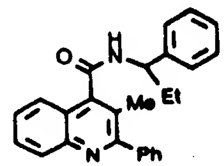
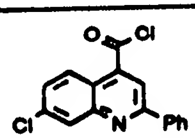
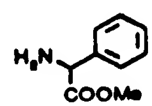
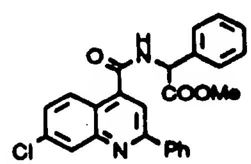
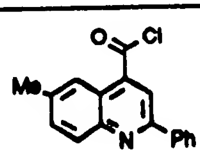
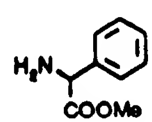
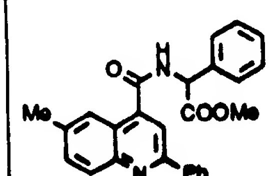
Ex.	Acyl chloride of (II)	(III)	(I)	Stereo chemi-stry	Molecular Formula	Molecular weight	Yield (%)	M.P. (°C) (cryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
29				(R,S)	$C_{25}H_{22}N_2O$	366.47	80	141-143 (toluene)	
30				(R,S)	$C_{26}H_{22}N_2O_3$	410.48	60	180-181 (toluene / iPr_2O)	
31				(R,S)	$C_{26}H_{24}N_2O$	380.49	55	156-158 (toluene/ esano)	
32				(R,S)	$C_{25}H_{19}ClN_2O_3$	430.90	48	180-183 (toluene)	
33				(R,S)	$C_{26}H_{22}N_2O_3$	410.48	48	179-181 (toluene)	

TABLE 2 (continues)

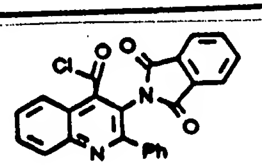
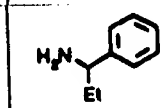
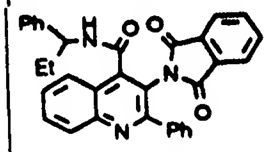
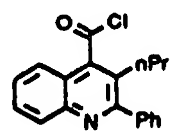
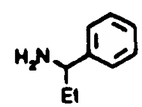
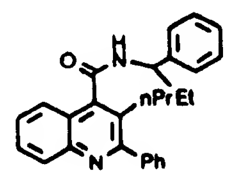
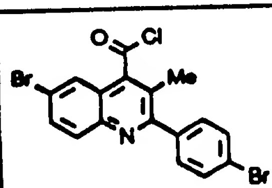
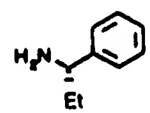
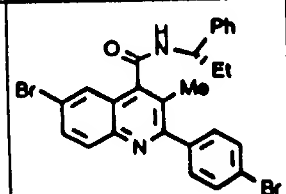
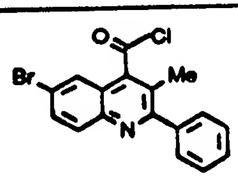
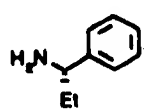
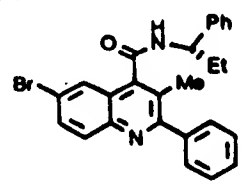
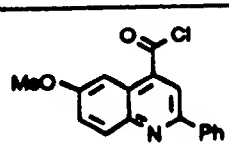
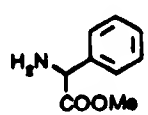
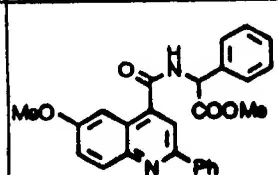
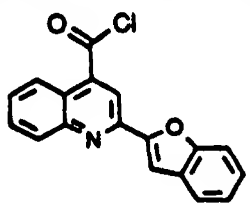
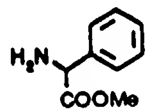
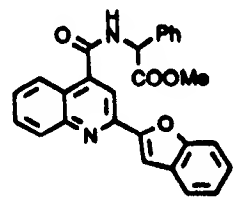
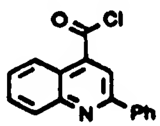
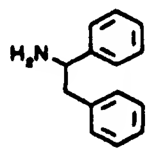
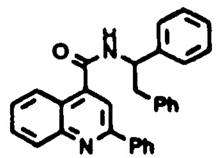
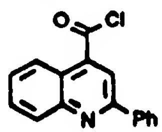
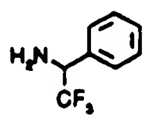
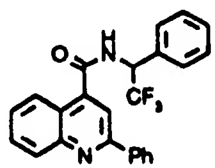
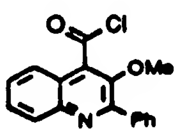
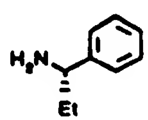
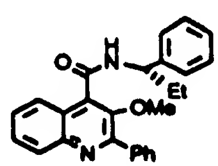
Ex.	Acyl chloride of (II)	(III)	(I)	Stereo chemistry	Molecular Formula	Molecular weight	Yield (%)	M.P. (°C) (cryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
39				(R,S)	$C_{33}H_{25}N_3O_3$	511.58	16	201-202 (toluene)	
40				(R,S)	$C_{28}H_{28}N_2O$	408.55	71	149-151 (toluene/ esano)	
41				(S)	$C_{26}H_{22}Br_2N_2O$	538.30	24	230-231 (Et_2O / iPr_2O)	- 49.8 (c=0.2)
42				(S)	$C_{26}H_{23}BrN_2O$	459.40	39	179-180 (esano/ iPrOH)	- 60.5
43				(R,S)	$C_{26}H_{22}N_2O_4$	426.48	45	209-211 (Me_2CO)	

TABLE 2 (continues)

Ex.	Acyl chloride of (II)	(III)	(I)	Stereo chemi-stry	Molecular Formula	Molecular weight	Yield (%)	M.P. (°C) (cryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
44				(R,S)	$C_{27}H_{20}N_2O_4$	436.47	65	240-241 (EtOAc)	
45				(R,S)	$C_{30}H_{24}N_2O$	428.53	47	194-196 (EtOAc)	
46				(R,S)	$C_{24}H_{17}F_3N_2O$	406.41	45	180-181 (toluene)	
47				(S)	$C_{26}H_{24}N_2O_2$	396.49	58	132-134 (Me_2CO)	- 45 (c=0.5)

The compounds of Examples 50-88 of general formula (I) (grouped together in the following Table 3) were prepared from the suitable reagents (II) and (III) represented in the table, following the synthesis procedure described in Example 5. The reaction yields were calculated on the purified, but not recrystallized, product. The analytical and spectroscopical data of Examples 50-88 are shown in Table 5.

TABLE 3

(I) ← (III) + (II)

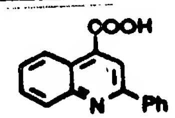
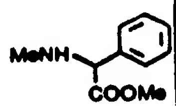
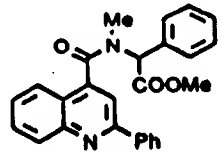
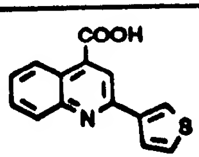
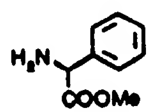
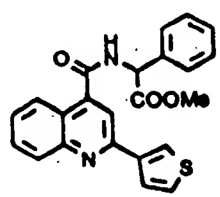
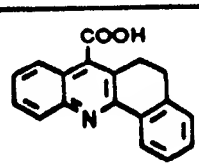
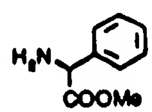
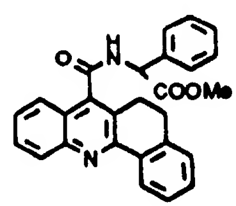
Ex.	(II)	(III)	(I)	Stereo chemistry	Molecular Formula	Molecular weight	Yield (%)	M.P. (°C) (cryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
50				(R,S)	$C_{26}H_{22}N_2O_3$	410.48	46	128-129 (iPrOH)	
51				(R,S)	$C_{23}H_{18}N_2O_3S$	402.47	88	169-171 (iPrOH)	
52				(R,S)	$C_{27}H_{22}N_2O_3$	422.49	41	217-219 (EtOH)	

TABLE 2 (continues)

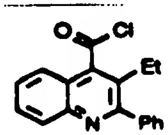
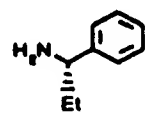
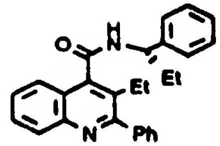
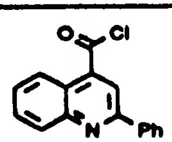
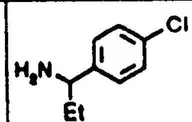
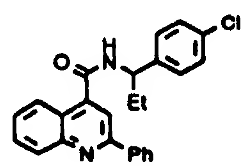
Ex.	Acyl chloride of (II)	(III)	(I)	Stereo chemistry	Molecular Formula	Molecular weight	Yield (%)	M.P. (°C) (cryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
48				(S)	$C_{27}H_{26}N_2O$	394.52	53	118-120 (hexane)	- 42 (c=0.5)
49				(R,S)	$C_{25}H_{21}ClN_2O$	400.91	40	177-178 (toluene)	

TABLE 3 (continues)

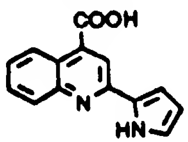
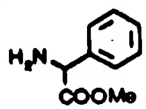
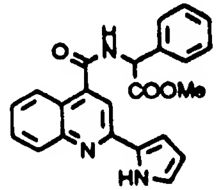
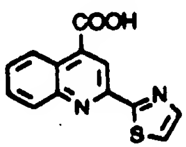
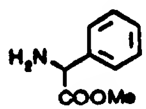
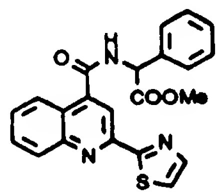
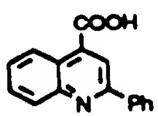
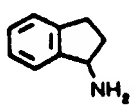
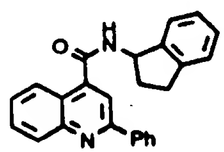
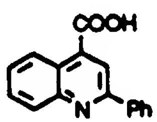
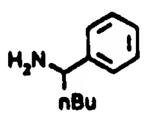
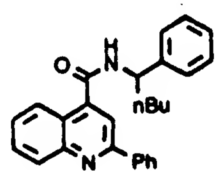
Ex.	(II)	(III)	(I)	Stereo chemistry	Molecular Formula	Molecular weight	Yield (%)	M.P. (°C) (cryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
53				(R,S)	$C_{23}H_{19}N_3O_3$	385.42	44	181-182 (iPrOH)	
54				(R,S)	$C_{22}H_{17}N_3O_3S$	403.45	50	209-211 (iPrOH)	
55				(R,S)	$C_{25}H_{20}N_2O$	364.45	95	183-184 (iPrOH)	
56				(R,S)	$C_{27}H_{26}N_2O$	394.52	77	155-156 (iPrOH/ iPr_2O)	

TABLE 3 (continues)

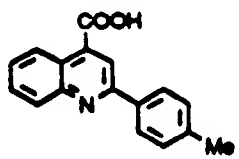
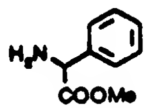
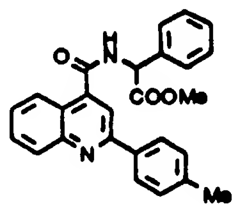
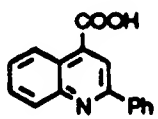
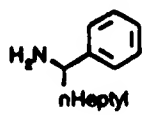
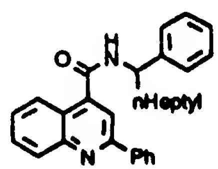
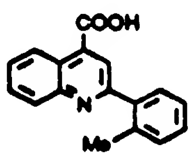
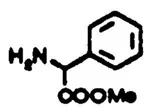
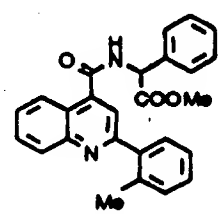
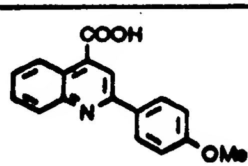
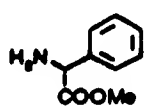
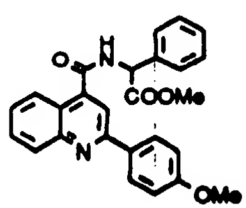
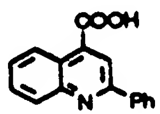
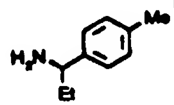
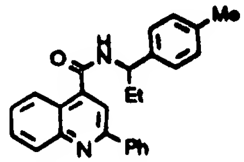
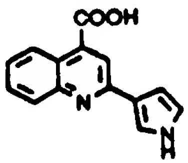
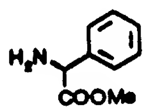
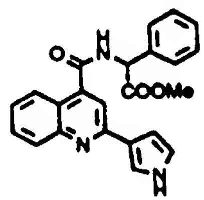
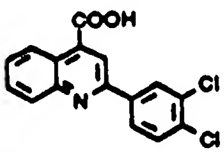
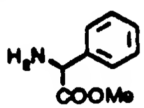
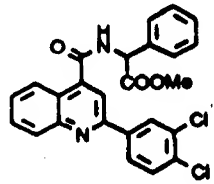
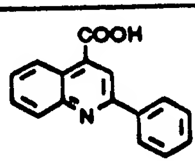
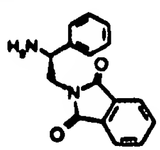
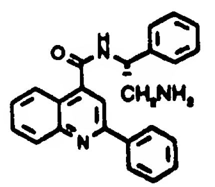
Ex.	(II)	(III)	(I)	Stereo chemi-stry	Molecular Formula	Molecular weight	Yield (%)	M.P.(°C) (cryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
57				(R,S)	$C_{26}H_{22}N_2O_3$	410.48	83	172-174 (iPrOH)	
58				(R,S)	$C_{30}H_{32}N_2O$	436.60	91	121-128 (iPr_2O)	
59				(R,S)	$C_{26}H_{22}N_2O_3$	410.48	79	180-182 (iPrOH)	
60				(R,S)	$C_{26}H_{22}N_2O_4$	426.48	62	182-183 (iPrOH)	

TABLE 3 (continues)

Ex.	(II)	(III)	(I)	Stereo chemistry	Molecular Formula	Molecular weight	Yield (%)	M.P. (°C) (cryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
65				(R,S)	$C_{26}H_{24}N_2O$	380.49	90	160-162 (iPrOH)	
66				(R,S)	$C_{23}H_{19}N_3O_3$	385.42	10	202-204 (iPr_2O)	
67				(R,S)	$C_{25}H_{18}Cl_2N_2O_3$	465.34	59	164-165 (iPrOH)	
68			 (a)	(R)	$C_{24}H_{21}N_3O$	367.45	49	139-141 (iPrOH/ iPr_2O)	- 6.9 (c=0.5)

(a) the phthalimido protective group was removed by refluxing for 4 hours with hydrated hydrazine in a 95% EtOH/1,2-dichloroethane 9:1 mixture; after that 37% HCl was added to pH = 1 and the reaction was refluxed for 1 hour.

TABLE 3 (continues)

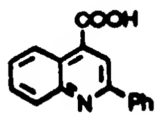
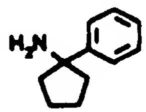
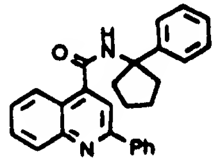
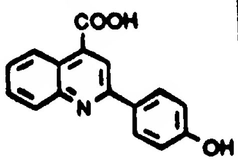
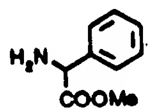
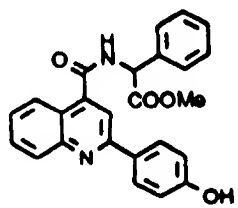
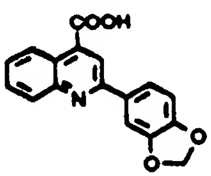
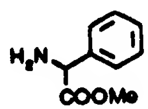
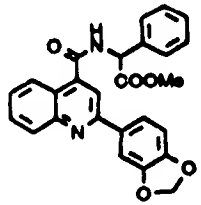
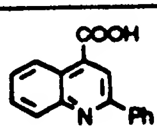
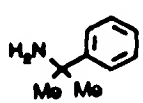
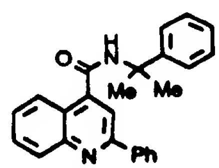
Ex.	(II)	(III)	(I)	Stereo chemistry	Molecular Formula	Molecular weight	Yield (%)	M.P. (°C) (cryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
61				--	$C_{27}H_{24}N_2O$	392.51	82	164-165 (iPrOH)	
62				(R,S)	$C_{25}H_{20}N_2O_4$	412.45	50	226-227 (iPrOH)	
63				(R,S)	$C_{26}H_{20}N_2O_5$	440.46	70	186-187 (iPrOH)	
64				--	$C_{25}H_{22}N_2O$	366.47	75	173-174 (iPrOH)	

TABLE 3 (continues)

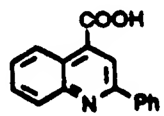
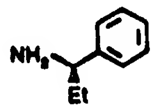
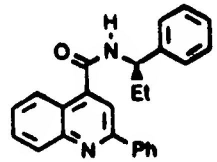
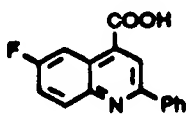
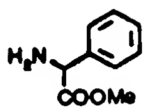
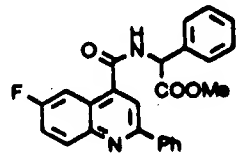
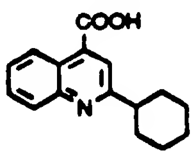
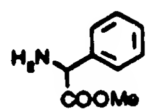
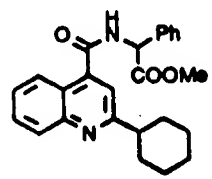
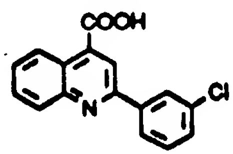
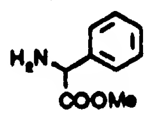
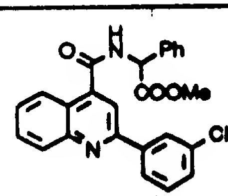
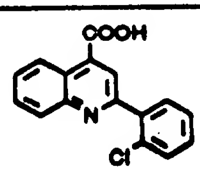
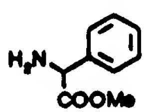
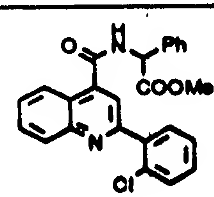
Ex.	(II)	(III)	(I)	Stereo chemi-stry	Molecular Formula	Molecular weight	Yield (%)	M.P. (°C) (cryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
74				(R)	$C_{25}H_{22}N_2O$	366.46	51	151-152 (iPrOH)	+ 26.6
75				(R,S)	$C_{25}H_{19}FN_2O_3$	414.44	44	174-176 (toluene/ EtOAc)	
76				(R,S)	$C_{25}H_{26}N_2O_3$	402.50	53	151-153 (EtOAc)	
77				(R,S)	$C_{25}H_{19}ClN_2O_3$	430.90	68	161-163 (toluene/ hexane)	
78				(R,S)	$C_{25}H_{19}ClN_2O_3$	430.90	43	175-178 (toluene/ hexane)	

TABLE 3 (continues)

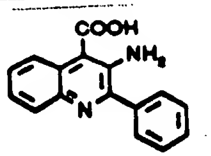
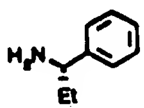
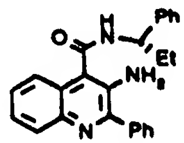
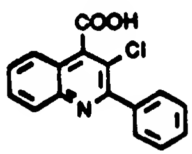
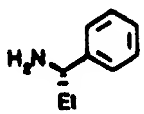
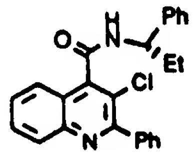
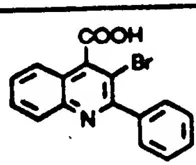
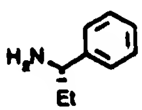
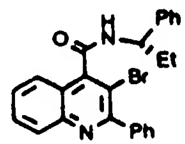
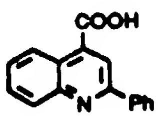
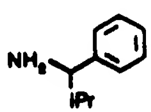
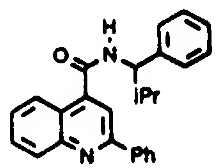
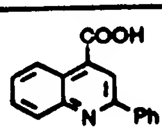
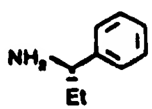
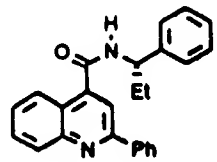
Ex.	(II)	(III)	(I)	Stereo chemi-stry	Molecular Formula	Molecular weight	Yield (%)	M.P. (°C) (cryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
69				(S)	$C_{25}H_{23}N_3O$	381.48	78	153-155 (iPrOH/ iPr_2O)	- 68.0 (c=0.5)
70				(S)	$C_{25}H_{21}ClN_2O$	400.91	58	137-139 (toluene/ hexane)	- 40.5 (c=0.5)
71				(S)	$C_{25}H_{21}BrN_2O$	445.37	20	119-122 (toluene/ hexane)	- 41.4 (c=0.5)
72				(R,S)	$C_{26}H_{24}N_2O$	380.49	59	165-166 (iPrOH)	
73				(S)	$C_{25}H_{22}N_2O$	366.46	77	140-141 (iPrOH)	- 26.7

TABLE 3 (continues)

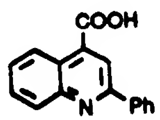
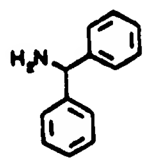
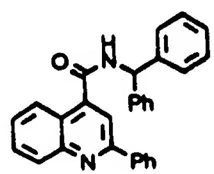
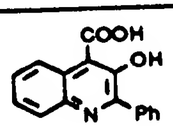
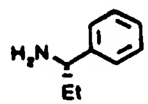
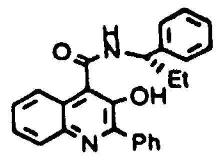
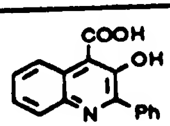
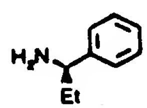
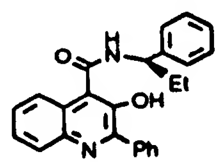
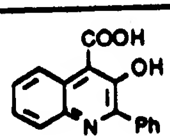
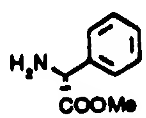
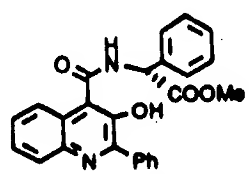
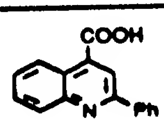
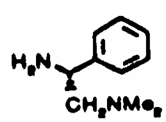
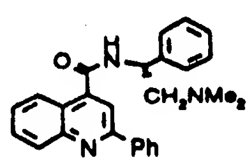
Ex.	(II)	(III)	(I)	Stereo chemistry	Molecular Formula	Molecular weight	Yield (%)	M.P.(°C) (cryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
84				--	$C_{29}H_{22}N_2O$	414.51	42	182-184 (EtOAc)	
85				(S)	$C_{25}H_{22}N_2O_2$	382.47	66	122-125 (iPr$_2$O)	- 28.4 (c=0.5)
86				(R)	$C_{25}H_{22}N_2O_2$	382.47	66	122-125 (esano/ EtOAc)	+ 27.2 (c=0.5)
87				(R)	$C_{25}H_{20}N_2O_4$	412.45	70	125-127 (iPr$_2$O)	- 50 (c=0.5)
88				(R)	$C_{26}H_{25}N_3O$	395.51	26	133-135 (iPr$_2$O/ iPrOH)	- 11.2 (c=0.5)

TABLE 3 (continues)

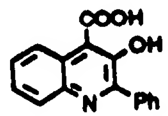
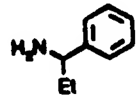
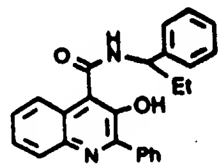
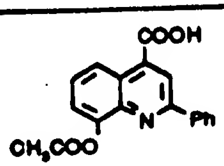
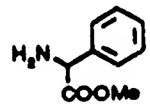
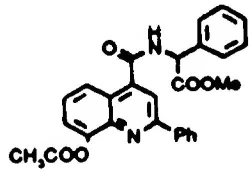
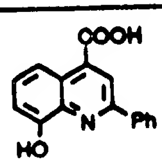
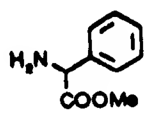
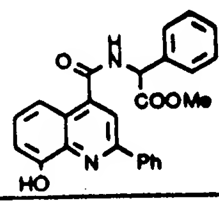
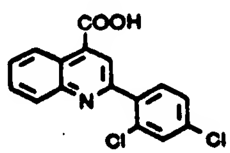
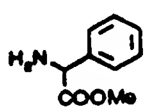
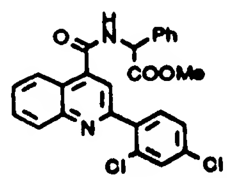
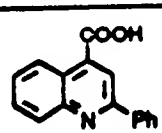
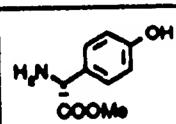
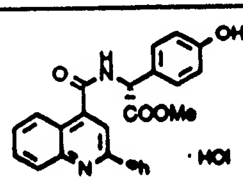
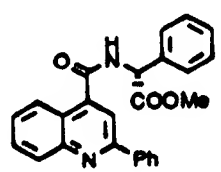
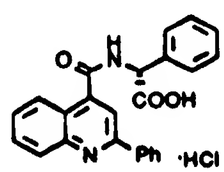
Ex.	(II)	(III)	(I)	Stereo chemistry	Molecular Formula	Molecular weight	Yield (%)	M.P. (°C) (cryst. solv.)	(c=1
79				(R,S)	$C_{25}H_{22}N_2O_2$	382.47	47	168-169 (toluene)	
80				(R,S)	$C_{27}H_{22}N_2O_5$	454.49	16	193-194 (toluene)	
81				(R,S)	$C_{25}H_{20}N_2O_4$	412.40	32	178-180 (toluene)	
82				(R,S)	$C_{25}H_{18}Cl_2N_2O_3$	465.34	61	142-143 (iPrOH)	
83				(R)	$C_{25}H_{20}N_2O_4 \cdot HCl$	448.88	50	140 dec. (Me_2CO)	-7

TABLE 4 (continues)

Ex.	(Ic)	(I)	Stereo chemi-stry	Molecular Formula	Molecular weight	Yield (%)	M.P. (°C) (cryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
92			(R)	$C_{24}H_{18}N_2O_3$ ·HCl	418.88	94	203-205 (acetone)	- 40.0 (c=0.5)

The compounds of Examples 88-92 of general formula (I) (grouped together in the following Table 4) were prepared from other compounds of formula (I) (more precisely from compounds of formula (Ic)), following the synthesis procedure described in Example 10 (for the compounds of Examples 89, 90 and 91) and in Example 9 (for the compound of Example 92).. The acid chlorides were prepared from the corresponding acids of formula (II), following Description 1. The reaction yields were calculated on the purified, but not recrystallized, product. The analytical and spectroscopical data of Examples 89-92 are shown in Table 5.

TABLE 4

(Ic) ⟶ (I)

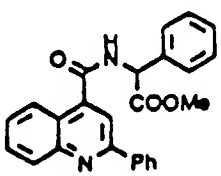
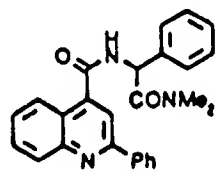
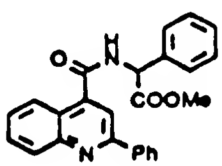
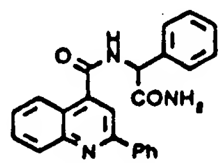
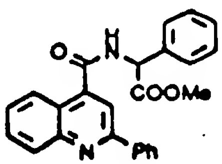
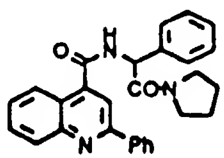
Ex.	(Ic)	(I)	Stereo chemistry	Molecular Formula	Molecular weight	Yield (%)	M.P. (°C) (cryst. solv.)	$[\alpha]_D^{20}$ (c=1, MeOH)
89			(R,S)	$C_{26}H_{23}N_3O_2$	409.49	22	219-221 (iPrOH /EtOH)	
90			(R,S)	$C_{24}H_{19}N_3O_2$	381.43	95	237-238 (iPrOH /EtOH)	
91			(R,S)	$C_{28}H_{25}N_3O_2$	435.53	69	199-200 (iPrOH)	

TABLE 5 (continues)

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200° C; 70 eV; 200 μA)	300 MHz ^1H NMR (DMSO), 303 K
22	Calc. C,82.07; H,6.36; N,7.36 Found C,81.95; H,6.33; N,7.30	3260; 1630; 1535	380 (M+.); 351; 246; 218	(353 K): 8.90 (d br,1H); 8.01 (d,1H); 7.72 (dd,1H); 7.65 (d br,1H); 7.60-7.49 (m,6H); 7.46 (d,2H); 7.38 (dd,2H); 7.24 (dd,1H); 5.12 (dt,1H); 2.30 (s,3H); 1.98-1.78 (m,2H); 0.99 (t,3H).
23	Calc. C,82.07; H,6.36; N,7.36 Found C,81.80; H,6.37; N,7.30	3260; 1630; 1535	380 (M+.); 351; 246; 218	(353 K): 8.90 (d br,1H); 8.01 (d,1H); 7.72 (dd,1H); 7.65 (d br,1H); 7.60-7.49 (m,6H); 7.46 (d,2H); 7.38 (dd,2H); 7.24 (dd,1H); 5.12 (dt,1H); 2.30 (s,3H); 1.98-1.78 (m,2H); 0.99 (t,3H).
24	Calc. C,73.22; H,5.20; N,6.57 Found C,72.88; H,5.25; N,6.44	3282; 1750; 1640; 1530	426 (M+.); 367; 277	9.65 (d,1H); 8.18 (d,1H); 8.11 (d,1H); 7.96 (s,1H); 7.83 (dd,1H); 7.81 (dd,1H); 7.66 (dd,1H); 7.54-7.46 (m,3H); 7.44-7.33 (m,3H); 7.22 (d,1H); 7.13 (dd,1H); 5.80 (d,1H); 3.87 (s,1H); 3.71 (s,3H).
25	Calc. C,84.13; H,5.92; N,6.33 Found C,82.28; H,5.86; N,6.19	3250; 1630; 1545	442 (M+.); 413; 308; 280	8.86 (d,1H); 8.13 (d,1H); 7.83 (dd,1H); 7.71-7.59 (m,2H); 7.31-7.14 (m,12H); 7.04 (d br,2H); 4.75 (dt,1H 1.58-1.42 (m,2H); 0.63 (t br,3H).
26	Calc. C,72.45; H,4.62; N,6.76 Found C,72.19; H,4.66; N,6.69	3320; 1745; 1650; 1595	414 (M+.); 355; 250; 222	9.70 (d,1H); 8.21 (d,1H); 8.16 (d,1H); 8.07 (dd,1H); 7.9 (d,1H); 7.86 (dd,1H); 7.72 (dd,1H); 7.64-7.55 (m,1H); 7.51 (dd,1H); 7.45-7.34 (m,4H); 5.80 (d,1H); 3,75 (s,3H).
27	Calc. C,69.03; H,4.62; N,6.44 Found C,68.97; H,4.63; N,6.43	3250; 1650; 1585; 1550	434 (M+.); 405; 232; 204	9.50 (d,1H); 8.31 (d,2H); 8.15 (d,1H); 8.10 (s,1H); 8.00 (d,1H); 7.81 (dd,1H); 7.72 (d,1H); 7.66 (d,1H); 7.64-7.52 (m,4H); 7.46 (dd,1H); 4.11 (dt,1H); 1.83 (dq,2H); 0.98 (t,3H).
28	Calc. C,78.24; H,5.47; N,7.60 Found C,78.49; H,5.58; N,7.41	3260; 1645; 1590; 1550	368 (M+.); 337; 232; 204	9.22 (d,1H); 8.33 (d,2H); 8.18 (s,1H); 8.13 (d,2H); 7.81 (dd,1H); 7.64-7.51 (m,4H); 7.46 (d,2H); 7.37 (dd,2H); 7.28 (dd,1H); 5.21 (dt,1H); 5.05 (t,1H); 3.71 (dd,2H).

TABLE 5. Analytical and spectroscopic data of Examples 16–92

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200° C; 70 eV; 200 μA)	300 MHz ^1H NMR (DMSO), 303 K
16		3240; 1750; 1640; 1595; 1545	398 (M+.); 232; 204	9.40 (d,1H); 8.30 (d,2H); 8.18 (d,1H); 8.13 (d,1H); 8.10 (s,1H); 7.83 (dd,1H); 7.66 (dd,1H); 7.63-7.51 (m,3H); 5.87 (s br,1H); 5.70 (m,2H); 5.12 (d,1H); 3.80 (s,3H); 2.92-2.60 (m,4H).
17	Calc. C,78.51; H,5.80; N,7.32 Found C,78.27; H,5.83; N,7.24	3400; 3200; 1640; 1595; 1532	337 $(M-C_2H_4OH)^+$; 232; 204	9.20 (d,1H); 8.31 (d,2H); 8.14 (d,1H); 8.08 (s,1H); 8.04 (d,1H); 7.82 (dd,1H); 7.64-7.51 (m,4H); 7.47 (d,2H); 7.37 (dd,2H); 7.27 (dd,1H); 5.10 (dd,1H); 4.81 (d,1H); 4.13 (dq,1H); 1.18 (d,3H).
18	Calc. C,78.76; H,6.10; N,7.07 Found C,78.60; H,6.08; N,7.00	3260; 3220; 1632; 1550 *	396 (M+.); 367; 262; 219	9.24 (d,1H); 8.07 (d,1H); 7.97 (dd,2H); 7.76-7.70 (m,1H); 7.62-7.51 (m,5H); 7.46 (d,2H); 7.39 (dd,2H); 7.29 (dd,1H); 5.10 (dt,1H); 3.52 (s,3H); 1.82 (dq,2H); 1.00 (t,3H).
19	Calc. C,82.43; H,7.16; N,6.63 Found C,82.31; H,7.20; N,6.58	3240; 1630; 1540	423 (MH+) *	(353 K): 8.89 (d br,1H); 8.00 (d,1H); 7.70 (dd,1H); 7.60-7.42 (m,9H); 7.36 (dd,2H); 7.28 (dd,1H); 5.13 (dt,1H); 2.66 (m,2H); 1.90 (ddq,2H); 1.30 (m,2H); 1.00 (t,3H); 0.95 (m,2H); 0.57 (t br,3H).
20	Calc. C,77.04; H,5.54; N,6.42 Found C,76.81; H,5.54; N,6.35	3290; 1760; 1645; 1590; 1532	436 (M+.); 377; 272; 271	(353 K): 9.50 (d,1H); 8.08 (d,1H); 7.88 (d,1H); 7.80-7.72 (m,2H); 7.60 (dd,1H); 7.52 (dd,2H); 7.47-7.30 (m,6H); 5.90 (d,1H); 2.60 (t,2H); 2.57 (t,2H); 2.26-2.06 (m,2H).
21	Calc. C,82.63; H,7.61; N,6.22 Found C,82.84; H,7.64; N,6.16	3270; 1635; 1550 *	450 (M+.); 421; 316	(373 K): 8.71 (d br,1H); 7.99 (d,1H); 7.70 (m,2H); 7.52-7.42 (m,8H); 7.37 (dd,2H); 7.27 (dd,1H); 5.12 (dt,1H); 2.67 (dd,2H); 1.91 (ddq,2H); 1.36-1.26 (m,2H); 1.12-1.02 (m,2H); 1.00 (t,3H); 1.00-0.90 (m,4H); 0.76 (t,3H).

TABLE 5 (continues)

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200° C; 70 eV; 200 µA)	300 MHz ^1H NMR (DMSO), 303 K
37	Calc. C,82.08; H,6.36; N,7.36 Found C,82.21; H,6.39; N,7.34	3300; 1635; 1590; 1545	380 (M+.); 337; 232; 204	9.28 (d,1H); 8.14 (d,1H); 8.07 (s,1H); 8.01 (d,1H); 7.82 (dd,1H); 7.64-7.51 (m,4H); 7.46 (d,2H); 7.39 (dd,2H); 7.28 (dd,1H); 5.15 (dt,1H); 1.94-1.69 (m,2H); 1.54-1.29 (m,2H); 0.95 (t,3H).
38	Calc. C,82.20; H,6.64; N,7.10 Found C,82.34; H,6.64; N,7.07	3240; 1640; 1550	395 (MH+); CI; gas reagent methaneP 5000 mTorr; source 150 °C	(353 K): 8.91 (d,1H); 8.00 (d,1H); 7.71 (dd,1H); 7.68-7.48 (m,7H); 7.45 (d,2H); 7.39 (dd,2H); 7.29 (dd,1H); 5.11 (dt,1H); 2.78-2.62 (m,2H); 2.00-1.80 (m,2H); 1.00 (t,3H); 0.90 (t br,3H).
39	Calc. C,77.48; H,4.93; N,8.21 Found C,77.25; H,4.99; N,8.07	3330; 1790; 1720; 1665; 1530	511 (M+.); 482; 377; 349; 321	(353 K): 8.90 (d,1H); 8.20 (d,1H); 7.94 (dd,1H); 7.88-6.90 (m,5H); 7.74 (d,1H); 7.69 (dd,1H); 7.48-7.42 (m,2H); 7.36-7.31 (m,3H); 7.25-7.20 (m,2H); 7.18-7.10 (m,2H); 4.85 (dt,1H); 1.73 (ddq,1H); 0.82 (t,3H).
40	Calc. C,82.32; H,6.91; N,6.86 Found C,82.02; H,6.95; N,6.90	3250; 1635; 1550	408 (M+.); 379, 289, 274; 246	(373 K): 8.72 (d,1H); 8.00 (d,1H); 7.70 (dd,1H); 7.55-7.42 (m,9H); 7.38 (dd,2H); 7.28 (dd,1H); 5.15 (dt,1H); 2.66 (dd,2H); 1.94 (ddq,2H); 1.33 (m,2H); 1.01 (t,3H); 0.56 (t,3H).
41	Calc. C,58.02; H,4.12; N,5.20; Br,29.69 Found C,58.14; H,4.18; N,5.22; Br,29.44	3250; 1650; 1540	537/539/541 (MH+) •	(353 K): 8.95 (d,1H); 7.96 (d,1H); 7.83 (dd,1H); 7.76 (d,1H); 7.71 (d,2H); 7.55 (d,2H); 7.45 (dd,2H); 7.39 (dd,2H); 7.30 (dd,1H); 5.10 (dt,1H); 2.92 (s,3H); 2.30 (s,3H); 1.88 (ddq,2H); 1.01 (t,3H).
42	Calc. C,67.98; H,5.04; N,6.10; Br,17.39 Found C,68.04; H,5.02; N,6.05; Br,17.26	3260; 1640; 1540	459/461 (MH+) •	(353 K): 8.94 (d br,1H); 7.96 (d,1H); 7.81 (dd,1H); 7.76 (d,1H); 7.60-7.49 (m,4H); 7.45 (d,2H); 7.40 (dd,2H); 7.30 (dd,1H); 5.10 (dt,1H); 2.30 (s,3H); 1.89 (ddq,2H); 1.01 (t,3H).
43	Calc. C,73.22; H,5.20; N,6.57 Found C,73.41; H,5.39; N,6.61	3200; 1750; 1665; 1620; 1520	426 (M+.); 367; 262; 234	9.70 (d,1H); 8.24 (d,2H); 8.08 (s,1H); 8.05 (d,1H); 7.61 (d,1H); 7.58-7.35 (m,9H); 5.80 (d,1H); 3.89 (s,3H); 3.74 (s,3H).

TABLE 5 (continues)

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200° C; 70 eV; 200 μA)	300 MHz ^1H NMR (DMSO), 303 K
29	Calc. C,81.93; H,6.05; N,7.64 Found C,81.79; H,6.06; N,7.62	3260; 1650; 1595; 1550	366 (M+.); 337; 232; 204	9.24 (d,1H); 8.30 (d,2H); 8.14 (d,1H); 8.09 (s,1H); 8.02 (d,1H); 7.82 (dd,1H); 7.63-7.51 (m,4H); 7.46 (d,2H); 7.38 (dd,2H); 7.24 (dd,1H); 5.14 (dt,1H); 1.95-1.78 (m,2H); 0.98 (t,3H).
30	Calc. C,76.08; H,5.40; N,6.83 Found C,75.88; H,5.37; N,7.08	3260; 1755; 1735; 1640; 1580; 1530	410 (M+.); 351; 261; 246; 217	9.70 (d,1H); 8.02 (d,1H); 7.76 (dd,1H); 7.70-7.47 (m,9H); 7.47-7.34 (m,3H); 6.82 (d,1H); 3.75 (s,3H); 2.32 (s br,3H).
31	Calc. C,82.08; H,6.36; N,7.36 Found C,81.82; H,6.34; N,7.33	3220; 1630; 1550	380 (M+.); 351; 246; 217	(353 K): 9.00 (d,1H); 8.01 (d,1H); 7.37 (dd,1H); 7.60-7.48 (m,7H); 7.45 (d,2H); 7.38 (dd,2H); 7.28 (dd,1H); 5.10 (dt,1H); 2.28 (s,3H); 2.00-1.80 (m,2H); 1.00 (t,3H).
32	Calc. C,69.69; H,4.45; N,6.50 Found C,69.58; H,4.49; N,6.49	3270; 1750; 1670; 1595; 1520	430 (M+.); 371;266; 238; 203	9.78 (d,1H); 8.29 (d,2H); 8.24 (d,1H); 8.19 (d,1H); 8.16 (s,1H); 7.73 (dd,1H); 7.61-7.49 (m,5H);7.47-7.36 (m,3H); 5.80 (d,1H); 3.79 (s,3H).
33	Calc. C,76.49; H,5.40; N,6.82 Found C,76.74; H,5.40; N,6.88	3240; 1750; 1665; 1590; 1510; 1500	410 (M+.); 351; 246; 218	9.70 (d,1H); 8.26 (d,2H); 8.08 (s,1H); 8.03 (d,1H); 7.96 (s,1H); 7.68 (dd,1H); 7.60-7.50 (m,5H); 7.48-7.36 (m,3H); 5.80 (d,1H); 3.79 (s,3H); 2.50 (s,3H).
34	Calc. C,78.51; H,5.79; N,7.32 Found C,78.78; H,5.78; N,7.23	3220; 1740; 1695; 1535	382 (M+.); 337; 232; 204	9.35 (d,1H); 8.32 (d,2H); 8.14 (d,1H); 8.11 (d,1H); 8.10 (s,1H); 7.84 (dd,1H); 7.64 (dd,1H); 7.61-7.54 (m,3H); 7.50 (d,2H); 7.40 (dd,2H); 7.30 (dd,1H); 5.41 (dt,1H); 3.73-3.60 (m,2H); 3.36 (s,3H).
35	Calc. C,69.69; H,4.45; N,6.50 Found C,70.27; H,4.46; N,6.45	3240; 1750; 1670; 1590; 1550; 1500	430 (M+.); 371; 266; 238; 203	9.80 (d,1H); 8.29 (d,2H); 8.27 (d,1H); 8.21 (s,1H); 8.16 (d,1H); 7.86 (dd,1H); 7.61-7.51 (m,5H); 7.48-7.38 (m,3H); 5.80 (d,1H); 3.75 (s,3H).
36	Calc. C,76.40; H,5.70; N,6.60 Found C,76.44; H,5.72; N,6.62	3240; 1760; 1640; 1540	425 (MH+) •	(353 K): 9.52 (d,1H); 8.01 (d,1H); 7.89 (s br,1H); 7.74 (dd,1H); 7.60 (dd,1H); 7.54-7.48 (m,7H); 7.44-7.33 (m,3H); 4.88 (d,1H); 3.78 (s,3H); 2.91-2.68 (m,2H); 0.91 (t,3H).

TABLE 5 (continues)

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200° C; 70 eV; 200 µA)	300 MHz ^{1}H NMR (DMSO), 303 K
51	Calc. C,68.64; H,4.51; N,6.96 Found C,68.52; H,4.53; N,6.94	3290; 1740; 1640; 1590; 1530	402 (M+.); 343; 238; 210	9.72 (d,1H); 8.47 (dd,1H); 8.15 (d,1H); 8.07 (d,1H); 8.05 (s,1H); 7.96 (dd,1H); 7.81 (dd,1H); 7.71 (dd,1H); 7.62 (dd,1H); 7.53 (d,2H); 7.46-7.36 (m,3H); 5.78 (d,1H); 3.78 (s,3H).
52	Calc. C,76.76; H,5.25; N,6.63 Found C,76.39; H,5.25; N,6.55	3250; 1750; 1660; 1590; 1520	422 (M+.); 258; 230	9.70 (d,1H); 8.45 (dd,1H); 8.18 (d,1H); 7.80-7.38 (m,11H); 5.83 (d,1H); 3.79 (s,3H); 3.20-2.80 (s br,4H).
53	Calc. C,71.68; H,4.97; N,10.90 Found C,71.39; H,4.99; N,10.81	3410; 3250; 1740; 1678; 1600 *	385 (M+.); 221; 193	11.68 (s br,1H); 9.71 (d,1H); 8.17 (d,1H); 7.99 (d,1H); 7.86 (s,1H); 7.66 (dd,1H); 7.58-7.35 (m,6H); 7.00 (s br,2H); 6.22 (s br,1H); 5.75 (d,1H); 3.73 (s,3H).
54	Calc. C,65.50; H,4.25; N,10.42 Found C,65.48; H,4.22; N,10.38	3300; 1755; 1645; 1585; 1530	344 (M-$COOCH_3$)+; 239; 211	9.82 (d,1H); 8.28 (s,1H); 8.19 (d,1H); 8.14 (d,1H); 8.10 (d,1H); 8.00 (d,1H); 7.88 (dd,1H); 7.73 (dd,1H); 7.53 (d,2H); 7.47-7.36 (m,3H); 5.80 (d,1H); 3.78 (s,3H).
55	Calc. C,82.39; H,5.53; N,7.69 Found C,82.31; H,5.52; N,7.65	3240; 1640; 1590; 1545	365 (MH)+ •	9.20 (d,1H); 8.31 (d,2H); 8.27 (d,1H); 8.16 (s,1H); 8.14 (d,1H); 7.85 (dd,1H); 7.68 (dd,1H); 7.62-7-46 (m,4H); 7.32-7.23 (m,3H); 5.69 (dt,1H); 3.08-2.85 (m,2H); 2.64-2.52 (m,1H); 2.10-1.96 (m,1H).
56	Calc. C,82.20; H,6.64; N,7.10 Found C,82.29; H,6.66; N,7.05	3270; 1640; 1590; 1540	394 (M+.); 337; 232; 204	9.12 (d,1H); 8.30 (d,2H); 8.14 (d,1H); 8.07 (s,1H); 8.02 (d,1H); 7.82 (dd,1H); 7.64-7.52 (m,4H); 7.46 (d,2H); 7.39 (dd,2H); 7.28 (dd,1H); 5.13 (dt,1H); 1.96-1.71 (m,2H); 1.48-1.27 (m,4H); 0.9 (t,3H).
57	Calc. C,76.08; H,5.40; N,6.82 Found C,75.92; H,5.44; N,6.77	3300; 1752; 1642; 1590; 1530	410 (M+.); 351; 246; 218; 203	9.74 (d,1H); 8.20 (d,2H); 8.18 (d,1H); 8.12 (d,1H); 8.08 (s,1H); 7.82 (dd,1H); 7.64 (dd,1H); 7.54 (d,2H); 7.47-7.36 (m,5H); 5.8 (d,1H); 3.79 (s,3H); 2.40 (s,3H).

TABLE 5 (continues)

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200° C; 70 eV; 200 μA)	300 MHz ^1H NMR (DMSO), 303 K
44	Calc. C,74.30; H,4.62; N,6.42 Found C,74.28; H,4.61; N,6.41	3200; 1750; 1660; 1590; 1550; 1525; 1500	436 (M+.); 337; 272; 244	9.80 (d,1H); 8.18 (d,1H); 8.11 (d,1H); 8.09 (s,1H); 7.90 (s,1H); 7.87 (dd,1H); 7.80 (d,1H); 7.77 (d,1H); 7.67 (dd,1H); 7.54 (d,2H); 7.47-7.31 (m,5H); 5.80 (d,1H); 3.78 (s,3H).
45	Calc. C,84.08; H,5.65; N,6.54 Found C,84.13; H,5.65; N,6.51	3320; 1635; 1590; 1530	337 $(M-C_7H_7)^+$; 232; 204; 91	9.32 (ABXY,1H); 8.22 (d,2H); 8.09 (d,1H); 7.78 (dd,1H); 7.77 (s,1H); 7.64-7.52 (m,6H); 7.50-7.28 (m,9H); 5.53 (ABXY,1H); 3.20 (ABXY,1H); 3.16 (ABXY,1H).
46	Calc. C,70.91; H,4.22; N,6.89; F,14.02 Found C,70.86; H,4.17; N,6.92; F,13.88	3300; 1655; 1590; 1540; 1500	406 (M+.); 386; 232; 204	10.15 (d,1H); 8.30 (dd,2H); 8.18 (d,1H); 8.10 (s,1H); 7.98 (d,1H); 7.86 (dd,1H); 7.75-7.42 (m,9H); 6.21 (m,1H).
47	Calc. C,78.74; H,6.10; N,7.06 Found C,78.72; H,6.10; N,7.01	3250; 1635; 1550; 1500	396 (M+.); 367; 262; 219	9.24 (d,1H); 8.07 (d,1H); 7.97 (dd,2H); 7.76-7.70 (m,1H); 7.62-7.51 (m,5H); 7.46 (d,2H); 7.39 (dd,2H); 7.29 (dd,1H); 5.10 (dt,1H); 3.52 (s,3H); 1.82 (dq,2H); 1.00 (t,3H).
48	Calc. C,82.18; H,6.64; N,7.10 Found C,81.93; H,6.64; N,7.05	3250; 1630; 1540; 1500	394 (M+.); 365; 275; 260	(353 K): 8.90 (d br,1H); 8.00 (d,1H); 7.70 (dd,1H); 7.56-7.42 (m,9H); 7.38 (dd,2H); 7.29 (dd,1H); 5.13 (dt,1H); 2.72 (m,2H); 1.90 (ddq,2H); 1.00 (t,3H); 0.90 (t br,3H).
49	Calc. C,74.90; H,5.28; N,6.99 Found C,74.67; H,5.33; N,7.03	3270; 1645; 1590; 1550; 1495; 770	400 (M+.); 371; 232; 204	9.20 (d,1H); 8.32 (d,2H); 8.08 (dd,2H); 8.06 (s,1H); 7.82 (t,1H); 7.65-7.40 (m,8H); 5.00 (dt,1H); 1.93-1.73 (m,2H); 0.98 (t,3H).
50	Calc. C,76.08; H,5.40; N,6.82 Found C,76.16; H,5.42; N,6.84	1750; 1640; 1595;1550	411 (MH+); 232; 204*	8.32 (d,2H); 8.16 (d,1H); 8.10 (s,1H); 7.88 (dd,1H); 7.71 (dd,1H); 7.60-7.42 (m,9H); 3.86 (s,3H); 2.56 (s,3H).

TABLE 5 (continues)

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200° C; 70 eV; 200 μA)	300 MHz ^1H NMR (DMSO), 303 K
65	Calc. C,82.07; H,6.36; N,7.36 Found C,82.15; H,6.36; N,7.41	3320; 1640; 1590; 1530	380 (M+.); 351; 232; 204	9.20 (d,1H); 8.29 (dd,2H); 8.14 (d,1H); 8.06 (s,1H); 8.03 (d,1H); 7.81 (dd,1H); 7.64-7.50 (m,4H); 7.34 (d,2H); 7.19 (d,2H); 5.00 (dt,1H); 2.30 (s,3H); 1.93-1.73 (m,2H); 0.98 (t,3H).
66	Calc. C,71.68; H,4.97; N,10.90 Found C,70.42; H,4.99; N,10.56	3360; 3240; 1750; 1630; 1600; 1560	385 (M+.); 326; 221; 193	11.20 (s br,1H); 9.65 (d,1H); 8.05 (d,1H); 7.93 (d,1H); 7.78 (s,1H); 7.70 (dd,1H); 7.67 (m,1H); 7.55-7.34 (m,6H); 6.87 (m,1H); 6.80 (m,1H); 6.77 (d,1H); 3.75 (s,3H).
67	Calc. C,64.53; H,3.90; N,6.02; Cl,15.24 Found C,64.59; H,3.95; N,5.94; Cl,15.03	3200; 1755; 1635; 1590; 1535	464 (M+.); 405; 300; 272; 237	9.70 (d,1H); 8.55 (d,1H); 8.30 (dd,1H); 8.22 (d,1H); 8.21 (s,1H); 8.17 (d,1H); 7.86 (dd,1H); 7.84 (d,1H); 7.70 (dd,1H); 7.54 (dd,2H); 7.47-7.36 (m,3H); 5.78 (d,1H); 3.74 (s,3H).
68		3300; 1635; 1590; 1530; 1495; 770	338; 337; 255; 233; 232; 204	9.18 (d br,1H); 8.35 (d,2H); 8.20 (s,1H); 8.13 (d,1H); 8.07 (d,1H); 7.81 (dd,1H); 7.63-7.51 (m,4H); 7.44 (d,2H); 7.38 (dd,2H); 7.28 (dd,1H); 5.08 (dt br,1H); 2.89 (d,2H); 1.60 (s br,2H).
69	Calc. C,78.71; H,6.08; N,11.01 Found C,78.45; H,6.10; N,10.96	3490; 3380; 3260; 1630; 1600	381 (M+.); 352;247; 219; 218	9.20 (d,1H); 7.87 (m,1H); 7.70 (d,2H); 7.59-7.26 (m,11H); 5.08 (dt,1H); 4.80 (s br, 2H); 2.81 (dq,2H); 0.95 (t,3H).
70	Calc. C,74.90; H,5.28; N,6.99; Cl,8.84 Found C,74.88; H,5.25; N,6.98; Cl,8.92	3230; 1640; 1550	400 (M+.); 371; 266; 238; 203	9.37 (d,1H), 8.10 (d,1H); 7.85 (dd,1H); 7.75-7.35 (m,12H); 5.07 (dt,1H);1.80 (dq,2H); 0.98 (t,,3H).

TABLE 5 (continues)

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200° C; 70 eV; 200 μA)	300 MHz ^{1}H NMR (DMSO), 303 K
58	Calc. C,82.53; H,7.39; N,6.42 Found C,82.59; H,7.45; N,6.39	3260; 1650; 1590; 1550; 1540	337 (M-C_7H_{15})+; 249; 232; 204	9.28 (d,1H); 8.29 (d,2H); 8.14 (d,1H); 8.07 (s,1H); 8.02 (d,1H); 7.82 (dd,1H); 7.64-7.52 (m,4H); 7.46 (d,2H); 7.38 (dd,2H); 7.28 (dd,1H); 5,14 (dt,1H); 1.98-1.71 (m,2H); 1.30-1.20 (m,10H); 0.86 (t br,3H).
59	Calc. C,76.08; H,5.40; N,6.82 Found C,76.21; H,5.40; N,6.79	3400-3100; 1742; 1665; 1590; 1530	410 (M+.); 261; 218	9.70 (d,1H); 8.22 (d,1H); 8.10 (d,1H); 7.84 (dd,1H); 7.70 (dd,1H); 7.67 (s,1H); 7.56 (d,1H); 7.50 (dd,2H); 7.45-7.33 (m,5H); 5.80 (d,1H); 3.78 (s,3H); 2.42 (s,3H).
60	Calc. C,73.22; H,5.20; N,6.57 Found C,72.89; H,5.20; N,6.48	3300; 1750; 1645; 1590; 1520	426 (M+.); 367; 262; 234; 219; 191	9.72 (d,1H); 8.25 (d,2H); 8.17 (d,1H); 8.09 (d,1H); 8.07 (s,1H); 7.80 (dd,1H); 7.62 (dd,1H); 7.54 (dd,2H); 7.46-7.36 (m,3H); 7.12 (d,2H); 5.80 (d,1H); 3.89 (s,3H); 3.75 (s,3H).
61	Calc. C,82.62; H,6.16; N,7.14 Found C,82.76; H,6.18; N,7.19	3230; 1640; 1590; 1550 *	392 (M+.); 249; 232, 204	9.00 (s,1H); 8.32 (dd,2H); 8,13 (d,1H); 8.05 (s,1H); 7.93 (d,1H); 7.81 (dd,1H); 7.64-7.52 (m,6H); 7.39 (dd,2H); 7.26 (dd,1H); 2.61-2.50 (m,2H); 2.10-2.00 (m,2H); 2.00-1.75 (m,4H).
62	Calc. C,72.80; H,4.89; N,6.79 Found C,72.86; H,4.91; N,6.75	3500-3100; 1750; 1670; 1640; 1590	412 (M+.); 353; 248; 220	9.90 (s,1H); 9.70 (d,1H); 8.14 (d,2H): 8.14 (d,1H); 8.06 (d,1H); 8.01 (s,1H); 7.78 (dd,1H); 7.60 (dd,1H); 7.53 (dd,2H); 7.46-7.35 (m,3H); 6.94 (d,2H); 5.80 (d,3H); 3.75 (s,3H).
63	Calc. C,70.90; H,4.58; N,6.36 Found C,70.73; H,4.59; N,6.35	3350; 1735; 1655; 1590	440 (M+.); 381; 276; 248	9.70 (d,1H); 8.17 (d,1H); 8.09 (d,1H); 8.06 (s,1H): 7.88 (d,1H); 7.85 (dd,1H); 7.80 (dd,1H); 7.62 (dd,1H); 7.42 (dd,2H); 7.46-7.36 (m,3H); 7.10 (d,2H); 6.13 (s,2H); 5.73 (d,1H); 3.73 (s.3H).
64	Calc. C,81.94; H,6.05; N,7.64 Found C,82.02; H,6.07; N,7.60	3220; 1640; 1590; 1545	366 (M+.); 351; 248; 232; 204	9.01 (s br,1H); 8.34 (dd,2H); 8.15 (s,1H); 8.13 (d,1H); 8.01 (d,1H); 7.81 (dd,1H); 7.66-7.52 (m,6H); 7.39 (dd,2H); 7.25 (dd,1H).

TABLE 5 (continues)

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200° C; 70 eV; 200 μA)	300 MHz ^1H NMR (DMSO), 303 K
78	Calc. C,69.69; H,4.44; N,6.50 Found C,69.90; H,4.42; N,6.57	3290; 1745; 1660; 1600; 1520	431(MH+); TSP, ammonium acetate (0.1 M)/acetonitrile 60 : 40 as eluent; source 250 °C	9.70 (d,1H); 8.24 (d,1H); 8.14 (d,1H); 7.87 (dd,1H); 7.77 (s,1H); 7.76-7.62 (m,3H); 7.58-7.48 (m,4H); 7.44-7.34 (m,3H); 5.80 (d,1H); 3.72 (s,3H).
79	Calc. C,78.51; H,5.80; N,7.32 Found C,78.55; H,5.82; N,7.26	3310; 3110; 1645; 1575; 1535	382 (M+.); 353; 264; 247; 219	9.80 (s,1H); 9.11 (d,1H); 8.00-7.94 (m,3H); 7.61-7.42 (m,8H); 7.38 (dd,2H); 7.28 (dd,1H); 5.06 (dt,1H); 1.82 (ddq,2H); 0.97 (t,3H).
80	Calc. C,71.36; H,4.88; N,6.16 Found C,71.39; H,4.88; N,6.17	3320; 1760; 1735; 1650; 1530	455 (MH)+ •	9.74 (d,1H); 8.24 (dd,2H); 8.17 (s,1H); 8.08 (dd,1H); 7.70-7.50 (m,7H); 7.46-7.35 (m,3H); 5.75 (d,1H); 3.75 (s,3H).
81	Calc. C,72.80; H,4.89; N,6.79 Found C,73.24; H,5.00; N,6.42	3360; 3300; 1745; 1650; 1600; 1560;	413 (MH)+ •	9,69 (d,1H); 9.68 (s,1H); 8.49 (d,2H); 8.12 (s,1H); 7.64-7.35 (m,10H); 7.18 (d,1H); 5.79 (d,1H); 3.77 (s,3H).
82	Calc. C,64.53; H,3.90; N,6.02 Found C,64.71; H,3.96; N,6.00	3240; 1740; 1645; 1595; 1550	464 (M+.); 405; 300; 272; 237	10.68 (d,1H); 8.25 (d,1H); 8.14 (d,1H); 7.88 (dd,1H); 7.82 (d,1H); 7.78 (s,1H); 7.74 (dd,1H); 7.74 (d,1H), 7.62 (dd,1H); 7.51 (d,2H); 7.44-7.33 (m,3H); 6.78 (d,1H); 3.74 (s,3H).
83	Calc. C,66.89; H,4.72; N,6.24; Cl,7.90 Found C,66.53; H,4.74; N,6.10; Cl,7.48	3180; 1750; 1660; 1645; 1610; 1535; 1510	412 (M+.); 353; 232; 204	9.62 (d,1H); 8.28 (d,2H); 8.22 (d,1H); 8.16 (d,1H); 8.11 (s,1H); 7.86 (dd,1H); 7.68 (dd,1H); 7.61-7.51 (m,3H); 7.30 (d,2H); 6.80 (d,2H); 5.61 (d,1H); 3.71 (s,3H).
84	Calc. C,84.03; H,5.35; N,6.76 Found C,83.27; H,5.64; N,7.05	3210; 1640; 1590; 1525	414 (M+.); 337; 232; 204	9.79 (d,1H); 8.30 (dd,2H); 8.15 (s,1H); 8.12 (d,1H); 8.02 (d,1H); 7.81 (dd,1H); 7.63-7.26 (m,14H); 6.52 (d,1H).
85	Calc. C,78.51; H,5.80; N,7.33 Found C,78.49; H,5.84; N,7.26	3370; 1625; 1525	382 (M+.); 264; 247; 219	9.80 (s,1H); 9.11 (d,1H); 8.00-7.94 (m,3H); 7.61-7.42 (m,8H); 7.38 (dd,2H); 7.28 (dd,1H); 5.06 (dt,1H); 1.82 (ddq,2H); 0.97 (t,3H).

TABLE 5 (continues)

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200° C; 70 eV; 200 μA)	300 MHz ^1H NMR (DMSO), 303 K
71	Calc. C,67.42; H,4.75; N,6.29; Br,17.94 Found C,67.57; H,4.80; N,6.31; Br,18.00	3240; 1640; 1545	444/446 (M+.); 415/417; 310/312; 203	9.35 (d,1H); 8.10 (d,1H); 7.85 (dd br,1H); 7.70-7.30 (m,12H); 5.05 (dt,1H); 1.81 (dq,2H); 0.99 (t,3H).
72	Calc. C,82.07; H,6.36; N,7.36 Found C,82.00; H,6.36; N,7.33	3240; 1630;1590; 1545	381 (MH)+ ; TSP, ammonium acetate,(50 mM)/acetonitrile 60 : 40 as eluent; source 250 °C	9.24 (d,1H); 8.29 (d,2H); 8.14 (d,1H); 8.01 (s,1H); 7.96 (d,1H); 7.81 (dd,1H); 7.64-7.51 (m,4H); 7.47-7.36 (m,4H); 7.29 (dd,1H); 4.90 (dd,1H); 2.19-2.02 (m,1H);1.08 (d,3H); 0.80 (d,3H).
73	Calc. C,81.94; H,6.05; N,7.64 Found C,79.33; H,5.82; N,7.34	3320; 1635; 1590; 1535	366 (M+.); 337; 232; 204	9.24 (d,1H); 8.30 (d,2H); 8.14 (d,1H); 8.09 (s,1H); 8.02 (d,1H); 7.82 (dd,1H); 7.63-7.51 (m,4H); 7.46 (d,2H); 7.38 (dd,2H); 7.24 (dd,1H); 5.14 (dt,1H); 1.95-1.78 (m,2H); 0.98 (t,3H).
74	Calc. C,81.94; H,6.05; N,7.64 Found C,82.08; H,6.09; N,7.59	3280; 1637; 1590; 1540	366 (M+.); 337; 232; 204	9.24 (d,1H); 8.30 (d,2H); 8.14 (d,1H); 8.09 (s,1H); 8.02 (d,1H); 7.82 (dd,1H); 7.63-7.51 (m,4H); 7.46 (d,2H); 7.38 (dd,2H); 7.24 (dd,1H); 5.14 (dt,1H); 1.95-1.78 (m,2H); 0.98 (t,3H).
75	Calc. C,72.45; H,4.62; N,6.76 Found C,72.28; H,4.59; N,6.79	3280; 1740; 1650; 1630; 1550	414 (M+.); 355; 250; 222	9.75 (d,1H); 8.28 (dd,2H); 8.21 (dd,1H); 8.2 (s,1H); 7.95 (dd,1H); 7.77 (ddd,1H); 7.61-7.50 (m,5H); 7.47-7.36 (m,3H); 5.80 (d,1H); 3.74 (s,3H).
76	Calc. C,74.60; H,6.51; N,6.96 Found C,74.32; H,6.50; N,6.90	1740; 1665; 1595; 1535	402 (M+.); 238; 210	9.61 (d,1H); 8.11 (d,1H); 7.99 (d,1H); 7.75 (dd,1H); 7.59 (dd,1H); 7.50 (d,2H); 7.47-7.35 (m,4H); 5.74 (d,1H); 3.72 (s,3H); 2.90 (tt,1H); 2.00-1.20 (m,10H).
77	Calc. C,69.69; H,4.45; N,6.50 Found C,69.81; H,4.45; N,6.54	3290; 1745; 1660; 1640; 1585; 1530	431 (MH+) •	9.71 (d,1H); 8.37 (s,1H); 8.30-8.15 (m,3H); 7.85 (dd,1H); 7.69 (dd,1H); 7.63-7.38 (m,8H); 5.79 (d,1H); 3.74 (s,3H).

EXAMPLE 93

(R,S)-N-[α-(Methoxycarbonyl)benzyl]-2-(p-chlorophenyl)-quinoline-4-carboxamide

2 g (7.0 mmol) of 2-(p-chlorophenyl)quinoline-4-carboxylic acid and 1.7 ml (15.4 mmol) of N-methylmorpholine are dissolved, under nitrogen, in 50 ml of anhydrous THF.

The solution is cooled to -20°C and 0.91 ml (7.0 mmol) of isobutyl chloroformate are added. After 20 minutes, 2.12 g (10.5 mmol) of methyl (R,S) phenylglycinate hydrochloride and 1.3 ml (11.9 mmol) of N-methylmorpholine, dissolved in 30 ml of anhydrous THF, are added; the reaction mixture is then stirred at room temperature overnight.

5 ml of H_2O are added and the reaction mixture is evaporated to dryness in vacuo. The residue is dissolved in Et_2O, washed with a $NaHCO_3$ saturated solution and the organic phase is dried over Na_2SO_4 and evaporated to dryness in vacuo.

The oily residue is purified by flash chromatography over silica gel 230-400 mesh, eluting with a hexane/isopropyl ether 7:3 mixture, to give 0.9 g of the crude product, which is recrystallized three times from $iPrO_2$/toluene to yield 0.5 g of the desired product.

$C_{25}H_{19}ClN_2O_3$

M.P. = 170-172°C

M.W. = 430.90

Elemental analysis: Calculated C, 69.72; H, 4.45; N, 6.50

Found C, 69.82; H, 4.47; N, 6.48

TABLE 5 (continues)

Ex.	Elemental analysis	IR (KBr); cm^{-1}	MS (EI; source 200° C; 70 eV; 200 μA)	300 MHz ^{1}H NMR (DMSO), 303 K
86	Calc. C,78.51; H,5.80; N,7.33 Found C,78.55; H,5.84; N,7.30	3270; 1650; 1630; 1570; 1535	382 (M+.); 264; 247; 219	9.80 (s,1H); 9.11 (d,1H); 8.00-7.94 (m,3H); 7.61-7.42 (m,8H); 7.38 (dd,2H); 7.28 (dd,1H); 5.06 (dt,1H); 1.82 (ddq,2H); 0.97 (t,3H).
87	Calc. C,72.80; H,4.89; N,6.79 Found C,72.12; H,4.88; N,6.63	3360; 1735; 1625; 1530	412 (M+.); 353; 248; 219	9.85 (s,1H); 9.63 (d br,1H); 7.97 (m,3H); 7.89 (d br,1H); 7.62-7.34 (m,10H); 5.75 (d,1H); 3.76 (s,3H).
88	Calc. C,78.96; H,6.37; N,10.62 Found C,78.63; H,6.39; N,10.65	3320; 1640; 1590; 1525; 770	395 (M+.); 232; 204	9.15 (d,1H); 9.30 (d,2H); 9.18 (dd, 2H); 8.06 (s,1H); 7.80 (t,1H); 7.70-7.20 (m, 9H); 5.30 (dt,1H); 2.75 (dd,1H); 2.45 (dd,1H); 2.70 (s,6H).
89	Calc. C,76.26; H,5.66; N,10.26 Found C,75.74; H,5.66; N,10.06	3280; 1660; 1635; 1590	409 (M+.); 337; 232; 204	9.40 (d,1H); 8.26 (d,2H); 8.22 (d,1H); 8.12 (d,1H); 8.05 (s,1H); 7.81 (dd,1H); 7.62 (dd,1H); 7.59-7.49 (m,5H); 7.43-7.33 (m,3H); 6.15 (d,1H); 3.00 (s,3H); 2.90 (s,3H).
90	Calc. C,75.57; H,5.02; N,11.02 Found C,75.23; H,5.12; N,10.88	3360; 3270; 1680; 1650; 1600	381 (M+.); 337; 232; 204	9.40 (d,1H); 8.31 (d,2H); 8.16 (s,1H); 8.15 (d,1H); 8.12 (d,1H); 7.81 (dd,1H); 7.78 (s br,1H); 7.64-7.50 (m,6H); 7.41-7.30 (m,3H); 7.23 (s br,1H); 5.71 (d,1H).
91	Calc. C,77.22; H,5.79; N,9.65 Found C,76.91; H,5.87; N,9.56	3220; 1660; 1620; 1590	436 (MH+); TSP, ammonium acetate(0.1 M)/acetonitrile 60 : 40 as eluent; source 250° C	9.48 (d,1H); 8.27 (d,2H); 8.23 (d,1H); 8.12 (d,1H); 8.06 (s,1H); 8.02 (dd,1H); 7.63 (dd,1H); 7.60-7.50 (m,5H); 7.45-7.33 (m,3H); 5.92 (d,1H); 3.82-3.71 (m,1H); 3.53-3.26 (m,2H); 3.16-3.08 (m,1H); 1.98-1.68 (m,4H).
92	Calc. C,68.82; H,4.57; N,6.69; Cl,8.46 Found C,68.42; H,4.60; N,6.56; Cl,8.22	1740; 1670; 1635; 1610; 1540	382 (M+.); 337; 204	9.64 (d,1H); 8.28 (d,2H); 8.22 (d,1H); 8.16 (d,1H); 8.13 (s,1H); 7.84 (dd,1H); 7.66 (dd,1H); 7.62-7.51 (m,5H); 7.46-7.34 (m,3H); 5.70 (d,1H).

*nujol; 'FAB POS, thioglycerol matrix, gas Xe, 8 KeV, source 50°C.

Elemental analysis: Calculated C, 73.22; H, 5.20; N, 6.57

Found C, 73.01; H, 5.20; N, 6.48

I.R. (KBr): 3210; 1750; 1635; 1625; 1590; 1530; 1515 cm^{-1}

300 MHz ^{1}H-NMR (DMSO-d_6): 9.65 (d, 1H); 8.28 (d, 2H); 8.21 (d, 1H); 8.14 (d, 1H); 8.10 (s, 1H); 7.84 (dd, 1H); 7.67 (dd, 1H); 7.61-7.49 (m, 3H); 7.44 (d, 2H); 6.98 (d, 2H); 4.70 (d, 1H); 3.79 (s, 3H); 3.76 (s, 3H).

MS (EI; source 200°C; 70 eV; 200 µA): 426 (M+.); 367; 232; 204.

EXAMPLE 95

(R,S)-N-[α-(Methoxycarbonyl)-α-(methyl)benzyl]-N-methyl-2-phenylquinoline-4-carboxamide hydrochloride

0.50 g (1.3 mmol) of (R,S)-N-[α-(methoxycarbonyl)-benzyl]-2-phenylquinoline-4-carboxamide (compound of Ex. 4) is dissolved, under nitrogen, in 10 ml of anhydrous DMF.

The solution is cooled to 0°C and 0.052 g (1.3 mmol) of 60% NaH are added; after 20 minutes a 0°C, the reaction is warmed to room temperature and 0.09 ml (1.4 mmol) of MeI are added. The reaction mixture is then stirred at room temperature overnight and, subsequently the procedure is repeated adding again 0.052 g (1.3 mmol) of 60% NaH and 0.1 ml (1.6 mmol) of MeI.

After 6 hours at room temperature, 10 ml of a NH_4Cl saturated solution are added and then the reaction mixture is evaporated to dryness. The residue is dissolved in CH_2Cl_2 and washed with water; the organic phase is then separated, dried over Na_2SO_4 and evaporated to dryness.

I.R. (KBr): 3280; 1740; 1670; 1635; 1590; 1530 cm^{-1}.

300 MHz ^{1}H-NMR (DMSO-d_6): 9.71 (d, 1H); 8.32 (d, 2H); 8.21 (d, 1H); 8.13 (d, 1H); 8.13 (s, 1H); 7.85 (dd, 1H); 7.67 (dd, 1H); 7.63 (d, 2H); 7.53 (dd, 2H); 7.46-7.38 (m, 3H); 5.79 (d, 1H); 3.74 (s, 3H).

MS (EI; source 200°C; 70 eV; 200 µA): 430 (M+.); 371; 266; 238; 203.

EXAMPLE 94

(R)-N-[α-(Methoxycarbonyl)-4-methoxybenzyl]-2-phenylquinoline-4-carboxamide

0.62 g (1.5 mmol) of (R)-N-[α-(methoxycarbonyl)-4-hydroxybenzyl]-2-phenylquinoline-4-carboxamide (compound of Ex. 83) is dissolved in 30 ml of anhydrous acetone and 2 ml of anhydrous DMF; 0.14 g (0.75 mmol) of K_2CO_3 are added and the reaction mixture is stirred for 30 minutes.

After that, 0.093 ml (1.5 mmol) of methyl iodide are added at room temperature and the reaction mixture is heated at 40°C for 4 hours. 0.104 g (0.75 mmol) of K_2CO_3 and 0.093 ml (1.5 mmol) of methyl iodide are added again and the mixture is heated to reflux for 6 more hours.

The reaction is then evaporated to dryness _in vacuo_ and the residue is dissolved in AcOEt and washed with H_2O. The organic phase is dried over Na_2SO_4 and evaporated again to dryness _in vacuo_. The residue is crystallized from Et_2O to give 0.45 g of the desired product.

$C_{26}H_{22}N_2O_4$

M.P. = 160-162°C

M.W. = 426.48

extracted with CH_2Cl_2; the organic phase is washed with H_2O, 20% citric acid, a $NaHCO_3$ saturated solution and again salt-saturated H_2O; the organic phase is then separated, dried over Na_2SO_4 and evaporated to dryness.

The oily residue is purified by flash chromatography over silica gel 230-400 mesh, eluting with a hexane/ethyl acetate 70 : 30 mixture, containing 0.5% conc. NH_4OH, to give 0.64 g of crude product, which is triturated with a i-Pr_2O/i-PrOH 2:1 warm mixture; the precipitate is filtered, washed and dried to give 0.5 g of the desired product.

$C_{25}H_{20}N_2O_2$

M.P. = 160-161°C

M.W. = 380.45

Elemental analysis: Calculated C, 78.93; H, 5.30; N, 7.36;

Found C, 79.01; H, 5.31; N, 7.27.

I.R. (KBr): 3400; 3265; 1725; 1660; 1640; 1592 cm^{-1}.

300 MHz ^1H-NMR (DMSO-d_6): 9.60 (d, 1H); 8.29 (d, 2H); 8.17 (d, 1H); 8.14 (d, 1H); 8.12 (s, 1H); 7.82 (dd, 1H); 7.65 (dd, 1H); 7.61-7.51 (m, 5H); 7.48-7.36 (m, 3H); 2.19 (s, 3H).

MS (EI; source 200°C; 70 eV; 200 μA): 380 (M+.); 337; 232; 204.

EXAMPLE 97

(R,S)-N-[α-(2-Hydroxyethyl)benzyl]-2-phenylquinoline-4-carboxamide

0.7 g (1.7 mmol) of (R,S)-N-[α-(methoxycarbonylmethyl)benzyl]-2-phenylquinoline-4-carboxamide (compound of Ex. 15) are dissolved, under nitrogen, in 50 ml of t-BuOH and 2 ml of MeOH and the reaction is heated to

The oily residue is purified by flash chromatography over silica gel 230-400 mesh, eluting with a hexane/ethyl acetate 3 : 2 mixture, containing 0.5% conc. NH_4OH, to give 0.18 g of the crude product, which is dissolved in Et_2O and treated with HCl/Et_2O to yield 0.15 g of the desired product.

$C_{27}H_{24}N_2O_3.HCl$

M.W. = 460.96

I.R. (KBr): 1745; 1640; 1610 cm^{-1}.

MS (EI; source 200°C; 70 eV; 200 μA): 424 (M+.); 365; 232; 204.

EXAMPLE 96

(R,S)-N-[α-(Methylcarbonyl)benzyl]-2-phenylquinoline-4-carboxamide

0.27 ml (3.1 mmol) of oxalyl chloride are dissolved, under nitrogen, in 2.3 ml of anhydrous CH_2Cl_2.

The solution is cooled to -55°C and 0.22 ml (3.1 mmol) of DMSO, dissolved in 0.7 ml of anhydrous CH_2Cl_2 are dropped therein, keeping the temperature below -50°C. The reaction is stirred at -55°C for 7 minutes, after that 0.97 g (2.5 mmol) of (R,S)-N-[α-(1-hydroxyethyl)benzyl]-2-phenylquinoline-4-carboxamide (compound of Ex. 17), dissolved in 25 ml of anhydrous CH_2Cl_2, are added, keeping the temperature from -50 to -55°C.

After 30 minutes at -55°C, 1.9 ml (13.6 mmol) of TEA are added without exceeding -40°C; the reaction is then slowly warmed to room temperature and stirred for a further 15 minutes.

The reaction is quenched with 5 ml of H_2O and

0.62 g (1.6 mmol) of (S)-N-(α-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide hydrochloride (compound of Ex. 85) are dissolved in 30 ml of anhydrous DMF.

0.58 g (4.0 mmol) of dimethylaminoethyl chloride hydrochloride and 0.56 g (4.0 mmol) of K_2CO_3 are added and the reaction mixture is heated to reflux for 20 hours.

K_2CO_3 is subsequently filtered off and the solution is evaporated to dryness in vacuo; the residue is dissolved in AcOEt, washed with H_2O and 20% citric acid. The aqueous phase is alkalinized with 2 N NaOH and extracted with AcOEt; then it is washed with salt-saturated water, separated, dried over Na_2SO_4 and evaporated to dryness.

The residue is purified by flash chromatography over silica gel 230-400 mesh, eluting with a CH_2Cl_2/MeOH 98 : 2 mixture, containing 0.4% conc. NH_4OH and subsequently with CH_2Cl_2/MeOH 86 : 10, containing 0.6% conc. NH_4OH, to give 85 mg of the crude product, which is dissolved in AcOEt and treated with HCl/Et_2O to yield 75 mg of the desired product.

$C_{29}H_{31}N_3O_2$.HCl

M.P. = 70°C dec.

M.W. = 490.05

I.R. (nujol): 3600; 3100; 1650; 1550 cm^{-1}.

300 MHz ^{1}H-NMR (DMSO-d_6): 10.28 (s br, 1H); 9.50 (d, 1H); 8.10 (d, 1H); 7.96 (dd, 2H); 7.78 (m, 1H); 7.67-7.61 (m, 2H); 7.61-7.51 (m, 3H); 7.49-7.39 (m, 4H); 7.33 (dd, 1H); 5.08 (dt, 1H); 3.90 (t, 2H); 2.96 (dt, 2H); 2.49 (s, 6H); 1.85 (m, 2H); 0.97 (t, 3H).

reflux.

60 mg (1.6 mmol) of $NaBH_4$ are added in 15 minutes to the boiling solution. The reaction mixture is heated to reflux for 6 hours, quenched with 5 ml of a NH_4Cl saturated solution and then evaporated to dryness *in vacuo*. The residue is dissolved in CH_2Cl_2 and washed with salt-saturated water; the organic phase is then separated, dried over Na_2SO_4 and again evaporated to dryness *in vacuo*.

The crude product is purified by flash chromatography on silica gel 230-400 mesh, eluting with a mixture of Et_2O containing 0.5% conc. NH_4OH, then recrystallized from i-PrOH to give 0.19 g of the desired product.

$C_{25}H_{22}N_2O_2$

M.P. = 167-169°C

M.W. = 382.47

Elemental analysis: Calculated C, 78.52; H, 5.80; N, 7.32;

Found C, 78.49; H, 5.79; N, 7.29.

I.R. (KBr): 3360; 1650; 1592 cm^{-1}.

300 MHz ^1H-NMR (DMSO-d_6): 9.30 (d, 1H); 8.31 (d, 2H); 8.13 (d, 1H); 8.10 (s, 1H); 8.03 (d, 1H); 7.81 (dd, 1H); 7.64-7.51 (m, 4H); 7.46 (d, 2H); 7.39 (dd, 2H); 7.29 (dd, 1H); 5.30 (dt, 1H); 4.61 (t, 1H); 3.61-3.41 (m, 2H); 2.11-1.86 (m, 2H).

MS (EI; source 200°C; 70 eV; 200 μA): 382 (M+.); 337; 232; 204.

EXAMPLE 98

(S)-N-(α-Ethylbenzyl)-3-(2-dimethylaminoethoxy)-2-phenylquinoline-4-carboxamide hydrochloride

MS (EI; source 200°C; 70 eV; 200 μA): 423 (M+.); 381; 334; 289; 261; 247; 218.

Following the procedures described in the above Examples, the compounds listed hereinbelow were prepared:

1) N-[α-(ethyl)benzyl]-3-hydroxymethyl-2-phenylquinoline-4-carboxamide;

2) N-[α-(ethyl)benzyl]-3-dimethylaminomethyl-2-phenylquinoline-4-carboxamide;

3) N-[1-(4-pyridyl)propyl]-2-phenylquinoline-4-carboxamide;

4) N-[α-(ethyl)benzyl]-5-hydroxy-3-methyl-2-phenylquinoline-4-carboxamide;

5) N-[α-(ethyl)benzyl]-7-hydroxy-3-methyl-2-phenylquinoline-4-carboxamide;

6) N-[α-(ethyl)benzyl]-3-(methylamino)-2-phenylquinoline-4-carboxamide;

7) N-[α-(ethyl)benzyl]-3-(3-dimethylamino)propoxy-2-phenylquinoline-4-carboxamide;

8) N-[α-(ethyl)benzyl]-3-(aminoethoxy)-2-phenylquinoline-4-carboxamide;

9) N-[α-(ethyl)benzyl]-3-(1-pyrrolidinyl)ethoxy-2-phenylquinoline-4-carboxamide;

10) N-[α-(methylcarbonyl)benzyl]-3-methyl-2-phenylquinoline-4-carboxamide;

11) N-[α-(ethyl)benzyl]-5-methyl-2-phenylquinoline-4-carboxamide;

12) N-[α-(ethyl)benzyl]-3,5-dimethyl-2-phenylquinoline-4-carboxamide.

MS (FAB POS, thioglycerol matrix, gas Xe, 8 KeV, source 50°C): 454 (MH+)

EXAMPLE 99

(S)-N-(α-Ethylbenzyl)-3-acetylamino-2-phenylquinoline-4-carboxamide

0.40 g (1.05 mmol) of (S)-N-(α-ethylbenzyl)-3-amino-2-phenylquinoline-4-carboxamide (compound of Ex. 69) is heated in 25 ml of acetic anhydride at 70°C for 1 hour and then at 100°C for a further 3 hours.

The reaction mixture is evaporated to dryness *in vacuo* and the residue is dissolved in AcOEt; the organic phase is washed with water, a $NaHCO_3$ saturated solution, salt-saturated water, dried over Na_2SO_4 and again evaporated to dryness *in vacuo*.

The crude product (0.39 g) is purified by flash chromatography over silica gel 230-400 mesh, eluting with a hexane/AcOEt/conc. NH_4OH 70:30:0.5 mixture, to give 0.2 g of a chromatographically pure product which is crystallized from acetone to yield 0.14 g of the desired product.

$C_{27}H_{25}N_3O_2$

M.P. = 268-269°C

M.W. = 423.52

Elemental analysis: Calculated C, 76.57; H, 5.95; N, 9.92;
Found C, 76.38; H, 5.98; N, 9.90.

I.R. (KBr): 3230; 1670; 1640; 1555; 1525 cm^{-1}.

300 MHz ^1H-NMR (DMSO-d_6): 9.65 (s, 1H); 9.05 (d, 1H); 8.10 (d, 1H); 7.80 (t, 1H); 7.70-7.50 (m, 4H); 7.45-7.20 (m, 8H); 5.08 (dt, 1H); 1.85 (m, 2H); 1.60 (s, 3H); 0.97 (t, 3H).

independently hydrogen or C_{1-6} linear or branched alkyl, or together from a $-(CH_2)_n-$ group in which n represents 3, 4, or 5; or R_1 together with R forms a group $-(CH_2)_q-$, in which q is 2, 3, 4 or 5.

R_3 and R_4, which may be the same or different, are independently hydrogen, C_{1-6} linear or branched alkyl, C_{1-6} alkenyl, aryl, C_{1-6} alkoxy, hydroxy, halogen, nitro, cyano, carboxy, carboxamido, sulphonamido, C_{1-6} alkoxycarbonyl, trifluoromethyl, acyloxy, phthalimido, amino, $-(CH_2)_r-NT_2$, in which r is 2, 3, or 4 and TR is hydrogen or C_{1-6} alkyl; $-O(CH_2)_s-OW_2$ in which is 2, 3, or 4 and W is hydrogen or C_{1-6} alkyl; hydroxyalkyl, aminoalkyl, mono- or di-alkyl-aminoalkyl, acylamino, alkylsulphonylamino, aminoacylamino, mono- or di-alkylaminoacylamino; with up to four R_3 substituents being present in the quinoline nucleous;

or R_4 is a group $-(CH_2)_t-$ when cyclized onto R_5 as aryl, in which t is 1, 2, or 3;

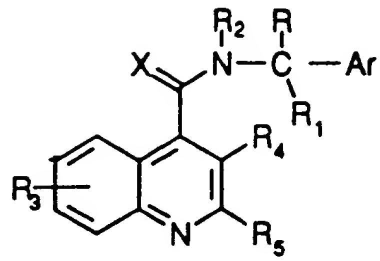
R_5 is branched or linear C_{1-6} alkyl, C_{3-7} cycloalkylalkyl, optionally substituted aryl, or an optionally substituted single or fused ring heterocyclic group, having aromatic character, containing from 5 to 12 ring atoms and comprising up to four hetero-atoms in the or each ring selected from S, O, N; X is O, S, or N-C≡N.

Milan, March 14, 1995.

The Mandatary
(Bracco Mauro)
of Studio Consulenza Brevettuale S.r.l.
signature

CLAIM

Compounds of formula (I):



(I)

in which:

Ar is an optionally substituted phenyl, naphtyl or C_{5-7} cycloalkdienyl group, or an optionally substituted single or fused ring heterocyclic group, having aromatic character, containing from 5 to 12 ring atoms and comprising up to four heteroatoms in the or each ring selected from S, O, N;

R is linear or branched C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkylalkyl, optionally substituted phenyl or phenyl C_{1-6} alkyl, optionally substituted five-membered heteroaromatic rings comprising up to four heteroatom selected from among O or N, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, C_{1-6} alkylaminoalkyl, di C_{1-6} alkylaminoalkyl, C_{1-6} acylaminoalkyl, C_{1-6} alkoxyalkyl, C_{1-6} alkylcarbonyl, carboxy, C_{1-6} alkoxycarbonyl, C_{1-6} alkoxycarbonyl C_{1-6} alkyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, di C_{1-6} alkylaminocarbonyl, halogeno C_{1-6}alkyl; or is a group $-(CH_2)_p-$ when cyclized onto Ar, where p is 2 or 3.

R_1 and R_2, which may be the same or different, are